THE EFFECTS OF BINGE DRINKING AND CANNABIS SMOKING POLYDRUG USE ON WORKING MEMORY AND EXECUTIVE FUNCTIONING.

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Abstract

The purpose of this thesis was to assess whether heavy social drinking cannabis and smoking polydrug use results in more significant working memory task impairment when compared to heavy social drinkers. Analysis of the academic literature indicated that both binge drinking and cannabis consumption acts as a depressant on the central nervous system. Resulting in impaired Neurotransmission and disruption to Long Term Potentiation, the process through which memories are formed and maintained. Both binge drinking and cannabis consumption result in structural alterations to the brain, specifically the prefrontal cortex and dorsolateral prefrontal cortex, which is associated with impairments to working memory and attendant executive functions.

The study began with a scoping search in the; The PsycInfo, Pubmed, cinall and Web of Science databases in which either 'binge drinking', cannabis, and the polydrug was paired, working memory, memory, executive functions, and the corresponding synonyms. Results identified nine papers on visuospatial working memory and nine on verbal working memory that were suitable for analysis. No statically significant effect for visuospatial working memory reported. However, there was a large and statistically significant mean weighted effect size showing lower task performance by the polydrug users for verbal working memory

A 3-participant group design with a control group consisting of (*N*= 28) non-binging alcohol users (CO) and two experimental groups of (*N*=20) binge drinkers (HSD) and (*N*=22) binge drinking-cannabis smoking polydrug users (HSDCC). The study recruited participants via opportunity sampling from Edge Hill University. Participants completed a battery of assessments, including a background and drugs history questionnaire. The study also employed a series of computerised working-memory and Executive Functions tests. The study measured the Haematological response via *f*NIRS. Results found significant between groups effects for IC, IR, VSWM and ESS (2 and 3 Back conditions) With the HSDCC group reporting quicker reaction times for IC. The study found no other significant between groups effects. Results reported no between-groups effects for *f*NIRS through a multivariate impact on the left hemisphere for the N-Back. The study did report a significant negative correlation between the use of cannabis and Oxy-Hb changes in the left inferior PFC related to task performance on the COWAT was reported.

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Importance as a research topic

Evidence from several countries indicates that heavy social drinking cannabis smoking polydrug use is the most common form of poly drug-taking behaviour worldwide. Reports from the United Kingdom in the 2015-16 Crime Survey for England and Wales estimated that over 9.6 million people aged 16 to 59 years had used cannabis whilst engaged in heavy social drinking at some time in their lives. The corresponding estimates for use in the last year and last month, respectively, were approximately 2.1 million and 1.1 million people. In each case, these were the most extensive estimates of consumption for any combination of drugs. In the United States, 8.3% of the population aged 12 years or older reported the use of cannabis whilst binge drinking in the past month in 2015. (Lader, 2016).

According to the European Monitoring Centre for Drugs and Drug Addiction [EMCDDA] (2017) frequent or heavy alcohol users were, in general, between two and six times more likely to report the use of cannabis compared to the general population and between two and nine times more likely to use cocaine. The strongest associations between intense alcohol and illicit drug use were in Cyprus, France, Italy, Portugal, and the weakest associations in those countries where frequent or heavy alcohol use is more widespread, such as Ireland and the United Kingdom (England and Wales). In France, the prevalence of cocaine use among frequent or heavy alcohol drinkers was 8 %, compared with just over 1 % in the general population, and in Italy, the corresponding figures were 27 % and 3 %.

The NIAAA (2016) reported that young people experience a dynamic and expanding drugs market, with an increasing range of (licit and illicit) psychoactive substances, or products made quickly and cheaply available. The expansion of the leisure and alcohol industry into areas of youth culture has also meant that, in many European countries, there

is now a critical mass of potential polydrug users who regularly gather in large numbers at music clubs and other nightlife settings (De Bellis et al., 2002). New technologies facilitate communication about drugs, their effects, where and how to get them, within and between social networks.

HSD cannabis smoking polydrug use dramatically increases the likelihood of adverse side effects occurring either physically (greening out) or psychologically (panic, anxiety and paranoia). Calafat et al. (2017) reported that over 35% of all road traffic accidents in 2009 were the result of individuals driving whilst under the influence of both alcohol and cannabis. While the negative effect that alcohol has on driving demonstrate that, cannabis use also affects a person's ability to concentrate and react in driving situations. Even at low doses, the combination of alcohol and cannabis is dangerous and places the drivers, their passengers and others on the road at serious risk (Louis-Martin (2017).

The importance of heavy social drinking and cannabis smoking as a topic for research lies in the combination of their relatively high prevalence amongst the general population. Reviews of scientific evidence highlight an association with impairments in neurocognitive performance (Broyd et al., 2016; Ganzer et al., 2016; Volkow et al., 2016). Changes in brain structures (Lorenzetti et al., 2013, 2016; Malchow et al., 2013; Rochetti et al., 2013), and changes in neurotransmission (Colizzi et al., 2016; Sami et al., 2015; Szabo, 2014). This evidence suggests that the relationship between alcohol and cannabis use to such impairments indicates that this form of drug-taking behaviour may serve as a significant public health issue. Decriminalising cannabis and the widespread coverage of this issue in the public domain only adds to the importance and relevance of research into the psychobiological implications of this form of polydrug use.

What is Alcohol?

Alcohol is the common term given for ethanol or ethyl alcohol, a chemical compound, ethanol is a volatile, flammable, colourless liquid with a slight characteristic odour. It is a psychoactive substance and is the primary type of alcohol found in alcoholic drinks. The natural fermentation of sugars produces ethanol, or through petrochemical processes. Ethanol is a popular recreational drug. As a central nervous system depressant, ethanol is

one of the most commonly consumed psychoactive drugs (Reusch 2015). It can lift mood, cause feelings of euphoria, decrease anxiety, and increase sociability and talkativeness. Alcoholic drinks, like wine, beer, cider and spirits, typically contain 1% to 50% of ethanol by volume. Alcoholic beverages sometimes feel like a stimulant (or even hallucinogen in some cases), but alcohol is a depressant. It inhibits the release of neurotransmitters in the brain, which slows down normal bodily responses (Robinson 2007).

The office for national statistics (2017) reported that 7% of adults in England regularly drink excessive amounts of alcohol, some 2.5 million people, who reported drinking over Chief Medical Officer's low-risk guidelines (less than 14 alcoholic units per week). In 2016, 79% of the population reported drinking regularly. In the UK, in 2015 there were 8,758 alcohol-related deaths (around 14 per 100,000 people). The mortality rates are highest among people aged 55-64. In England, there are an estimated 595,131 dependent drinkers, of whom only 108,696 are currently accessing treatment. Alcohol misuse is the most significant risk factor for death, ill-health and disability among 15-49-year-olds in the UK, and the fifth-biggest risk factor across all ages. Alcohol harms are estimated to cost the NHS around £3.5 billion annually. While the price of alcohol has increased by 36% since 2005, it remains 60% more affordable than it was in 1980.

Burton et al. (2016) reported that alcohol is a causal factor in more than 60 medical conditions, including mouth, throat, stomach, liver and breast cancers; high blood pressure, cirrhosis of the liver; and depression in the UK in 2014-5. There were an estimated 1.1 million hospital admissions related to alcohol consumption, where an alcohol-related disease, injury or condition was the primary reason for hospital admission or a secondary diagnosis. In the same period, there were 339,000 admissions for problems directly caused by alcohol (Public Health England 2017). Males accounted for approximately 65% of all alcohol-related deaths in the UK in 2014. The alcohol-related mortality rate of men in the most disadvantaged socio-economic class is 3.5 times higher than for men in the least impoverished class. At the same time, for women, the figure is 5.7 times higher (Siegler et al. 2011). In England and Wales, an alcohol-induced liver disease caused 63% of all alcohol-related deaths in 2014. Liver disease is one of the few major causes of premature mortality that is increasing, and deaths have increased by around 40% in a decade (Williams et al., 2017). Between the ages of 60 and 74 admitted

to hospitals in England with mental and behavioural disorders associated with alcohol. Use has risen by over 150% in the past ten years, while the figure for 15-59 years old has increased by 94%

What is binge drinking?

Binge drinking or heavy social drinking (HSD) is heavy episodic consumption of alcohol within a short period followed by a period of abstinence, precisely four or more drinks for a woman and five or more for a man (Squeglia et al. 2012). Other, less common definitions are blood alcohol concentration (BAC). For example, the National Institute on Alcohol Abuse and Alcoholism (NIAAA 2013) defines the term "binge drinking" as a pattern of drinking that brings a person's blood alcohol concentration (BAC) to 0.08%. In the United States, the term "extreme drinking" or "industrial-strength bingeing" is sometimes used to describe a more severe form of (single-evening) binge drinking; is defined as ten or more standard American drinks on a single occasion (sometimes as eight glasses for women). If done over 2 to 3 hours, a typical adult would have a peak BAC of at least 0.20 % (White 2006).

In summary, therefore, whilst the precise numerical definition used is open to debate, binge drinking consists of massive or rapid alcohol consumption over a short period with the explicit intention of becoming intoxicated. Notably, four or five drinks consumed over a whole day as an accompaniment to meals will not have the same effect as the same amount consumed over a couple of hours on an empty stomach (British Medical Association 2013).

The Office for National Statistics (2014) reported that of the 28.9 million people who said that they drank alcohol, 12.9 million (45%) engaged in binge drinking behaviour, drinking more than 4.67 units (around 2 pints of 4% beer or two medium (175 millilitres) glasses of 13% wine) on their most intense drinking day. Of these, 2.5 million (9%) drank more units in one day than the weekly recommended amount of 14 units (6 pints of beer or 1.4 bottles of 13% wine). Young people were less likely to have consumed alcohol; less than half (48%) of those aged 16 to 24 reported drinking alcohol in the previous week, compared with 66% of those aged 45 to 64. While overall being less likely to drink

alcohol, young drinkers were more likely than any other age group to consume more than the weekly recommended limit in one day. Among 16 to 24-year-old drinkers, 17% finished more than 14 units compared with 2% of those aged 65 and over.

What is cannabis?

Three varieties of cannabis belonging to the genus' cannabis', specifically Sativa, Indica, and Ruderalis have are known. Whether these different strains represent specific taxonomic categories or a single species is far from equivocal (de Meijer, 2014; Gloss, 2015; Hilig & Mahlberg, 2004). Cannabis is the common term given to the recreationally used drug derived from the plant (Both buds and leaves). In North America, the label 'marijuana' is the drug, rather than cannabis (NIDA, 2016). Recreational use of cannabis takes the form of smoke inhalation via cannabis "joints", although oral administration in the form of 'cakes' or 'tea' is also standard (Heustis & Smith, 2014). Traditionally, cannabis is processed through sieving the plant into a powder and then compressed and heated, a concrete block which referred to as cannabis resin, which is then self-administered through smoke inhalation (Advisory Council on the Misuse of Drugs, 2008; NIDA, 2016). The inhalation of vapour from the heating of an oil extract from the leaves of the cannabis plant sometimes referred to as dabbing, has developed as a means of self-administration in recent years, partly because the process of producing the oil leads to a relatively potent form of cannabis (Krauss et al., 2015; Loflin & Earleywine, 2014). The commonly self-reported desired effects of cannabis consumption include increased feelings of relaxation, an elevated mood level, and enhancements in sensory perception (Grinspoon et al., 2005; Winstock et al., 2010). The clinical administration of cannabis-based medications may include oral ingestion, sublingual, rectal, dermal, eye drops, and intravenous routes (Heustis & Smith, 2014; Scuderi et al., 2009).

The number of separately identified compounds isolated from the Cannabis Sativa plant has grown steadily since the 1980s, with 545 identified compounds (Elsohly & Gul, 2014). This total of 545 included 104 identified as being cannabinoids by their structure. This group of cannabinoids consists of those compounds considered to be psychoactive, most notably Δ9-tetrahydrocannabinol (Δ9-THC) (Pertwee, 1988). As this cannabinoid is chiefly responsible for the psychoactive effects of cannabis, descriptions of the potency of cannabis are generally related to the Δ9-THC concentration of a given supply (Freeman

et al., 2014; Hardwick & King, 2008). It is the high Δ9-THC concentration of the oil extracted from cannabis plant products for vapour inhalation, which makes it a potent form of the drug (Loflin & Earleywine, 2014). The breeding of cannabis plants and the use of cuttings from the flowering tops produce cannabis with elevated levels of Δ9-THC. Sometimes referred to as sinsemilla, or colloquially by users as 'skunk', this has become increasingly prevalent for consumption by smoking since the 1990s in the United Kingdom (Freeman et al., 2014; Hardwick & King, 2008), the United States (ElSohley et al., 2016), and Australia (Swift et al., 2013). Δ9-THC activates dopaminergic activity in the ventral tegmental and substantia nigra, which are both implicated in neural substrates relevant to substance addiction generally (French et al., 1997). The bioavailability level of THC consumed through cannabis smoking is approximately 25%, although much variability in this measure can be found both within and between individuals (Heustis & Smith, 2014).

There is evidence for a relationship between cannabis consumption and deleterious effects concerning neurotransmission and the integrity of neural structures, and cognitive performance. However, there is also evidence that cannabinoids can also be neuroprotective in some instances. Indeed, the existence of an endogenous cannabinoid system (ECS) may reasonably imply some benefits for human functioning and wellbeing through the activation of neuronal receptors for cannabinoid compounds. Capasso (2017) provides a brief background to the development of knowledge concerning the ECS and presents evidence that CBD, in particular, may have neuroprotective effects which protect against epilepsy. The mediation of glutamatergic activation is the likely basis for this neuroprotective effect. However, concomitant cannabis use by human users of ecstasy (MDMA) has not shown any neuroprotective effects such as may be implied by reductions in impaired cognitive performance compared to ecstasy users without concomitant cannabis use (Fisk et al., 2006). In this context, it is worth noting that low dose administrations of Δ9-THC have is a potential treatment for age-related cognitive decline in humans due to evidence emerging from a variety of rodent studies (Sarne, 2005).

What is polydrug use?

The term polydrug use is a blanket term for different types of specific drug-taking behaviour, several precise definitions of what polydrug use is, must, therefore, be considered. At one extreme is the notion of planned use, which is where the combined effects of multiple drugs elicit the desired result. According to the European Monitoring Centre for Drugs and Drug Addiction (2002) (EMCDDA) the term planned polydrug use, also referred to as CDI or combined drug intoxication, refers to the act of ingesting two or more psychoactive substances to achieve a combined effect. It is often the case that one drug is a base or primary narcotic, with the additional used to heighten the psychotropic effect. These drugs also act in a compensatory capacity for the side effects of the primary narcotic, thus making the experience more enjoyable with pharmacologically synergistic effects. The EMCDDA (2009) describe the behaviour as chaotic. The use of several substances simultaneously or consecutively. Boyes et al. (1999) were able to catalogue some of the different polydrug combinations; Ecstasy, combined with GBL, heroin with methadone, and alcohol with cannabis. Ives and Gehoni (2006) note an increase in the range and availability of drugs; this has increased the prevalence of illicit polydrug use worldwide. Coupled with a societal shift towards increased acceptability of polydrug use, means that this is becoming an area of increased interest for research.

Polydrug use often takes place in the context of recreational activities, with population surveys confirming that drug use is associated with visiting bars and nightclubs. Studies conducted in targeted nightlife settings during the past decade in several European countries have found comparatively high levels of polydrug use. Studies conducted in recreational settings indicates that lifetime prevalence estimates range from 15 % to 71 % for alcohol and ecstasy use and from 17 % to 68 % for amphetamine use. Tobacco (48 %), alcohol (11 %) and cannabis (9 %) were overall the substances most commonly used together regularly (five or more days a week); fewer than 1 % of respondents reported regular use of other substances. However, the study identified the existence of a tiny group of drug users who consumed drugs in a too intensive manner. It found that concomitant alcohol use was expected, with 34 % of those interviewed reported having been drunk more than twice during the four weeks before the interview. Drunkenness is likely to increase the risk of making ill-considered decisions about drug-taking and

engaged in by more males than females: 42 % and 27 % respectively (European Commission, 2007).

In the context of recreational drug-taking, polydrug use can be limited and linked to a specific social situation or location. For example, surveys conducted among 868 tourists at Ibiza airport reported that those who were already using drugs in the United Kingdom had a significantly higher frequency of polydrug use during the holiday period. Some 6.7 % reported using ecstasy for five nights or more while in the United Kingdom, compared with 36.9 % while in Ibiza; on average consumers used at least two illicit drugs during the holiday (for example, 46 % of ecstasy users also used cocaine) as well as alcohol (Bellis et al., 2008). Furthermore, some individuals who had never used illicit drugs at home started using while on holiday. An EMCDDA' Selected issue' on recreational drug use reported that 23 % of the young people surveyed had tried illicit drugs for the first time while abroad (EMCDDA, 2006). Evidence suggests that during short holiday periods and weekends, young people are particularly liable to indulge in poly drug-related activities. This pattern highlights the need for specifically targeted prevention and harm-reduction responses that take into account the context in which polydrug use occurs (De Bellis et al., 2003).

Polydrug use, proposed implications for neurotransmission

Evidence from within the psychobiological literature has demonstrated that the psychoactive agents in cannabis (THC) and alcohol (ethanol) can exert their effects upon psychological functions and attendant behaviours by disruption to neural communication. (Murphy et al., 2018; Marinkovic et al., 2019). It is important to note that ethanol is purely an exogenous substance entering the body via the consumption of alcoholic drinks alone (Schleur et al. 2019). Pharmacological research has demonstrated that ethanol has an affinity for both NMDA and Glutamate receptor sites (Lu et al. 2019, De Ternay, et al. (2019). Therefore alcohols influence upon neurotransmission can be seen as a function of ethanol's ability to serve as both an agonist and antagonist to these structures (Ranson et al. 2019). However, to appreciate THC's effects, Endogenous cannabinoids are compounds that are created within the central nervous system (CNS) and play a central role in the modulation of the CNS's monoamine functioning (Van Bockstale, 2013). Like ethanol, exogenous cannabinoids such as THC enter the body via external means,

predominantly through the smoking of cannabis cigarettes. Psychopharmacological research has been able to demonstrate that both exogenous and endogenous cannabinoids have an affinity for the cannabinoid receptors found within the brain. Exogenous cannabinoids, including THC, exert their influence on psychological functioning by disrupting neurotransmission at these cannabinoid receptors cites (Pertwee and Cascio, 2014).

Neuroanatomical research has identified two receptor sites of particular interest for an investigation into disruption to neural communication and HSD, specifically The N-methyl-D-aspartate receptor (NMDR) and the GABAA receptor (GABAAR). Both GABBAR and NMDR receptors are prominent throughout the brain. NMDRs ubiquity is a function of its role as a receptor for the minds primary excitatory neurotransmitter, glutamate whilst GBBAAR's ubiquity is a function of its role as a receptor for the primary inhibitory neurotransmitter GABA (Brassai et al. 2015). Alcohols influence upon neural communication is a function of decreased excitatory and increase inhibitory neurotransmission. (Petroff et al., 2002). To date, two cannabinoid receptors have been identified, referred to as cannabinoid receptor 1 and 2 or CB1 and CB2. These two primary G-protein receptors located within the endocannabinoid system (ECS). Whilst the role of the CB2 receptor is still largely to be elucidated upon, CB1's position is understood more clearly. CB1 receptors are on presynaptic axon terminals; the CB1 receptor-mediated synaptic inhibition. Since THC exerts an influence over the CB1 receptor, it is logical to conclude, therefore that THC's effect over neurotransmission is one of influencing neuronal inhibition (Murphy, 2018). It is also worth noting that while pharmacological research has almost exclusively focused on THC related activity at CB1 and CB2 receptor sites, there are other receptors throughout the body that are cannabinoid receptors (Russo et al., 2013). In a recent review examining THC's affinity for the CB1 and CB2 binding, Pertwee and Cascio (2014) reported that THC could be a partial agonist on both receptor sites. The authors note the more significant agonistic effects being for the synthetic THC, Nabilone, used in the treatment of multiple sclerosis (Wright and Guy, 2014).

While the receptors associated with alcohol consumption within all regions of the brain, it is logical to assume that in consideration of the effects of HSD cannabis smoking

polydrug research use should focus on those regions of the brain with a high density of CB1 receptors. Neuroanatomical research emphasises the importance of consideration of the pharmacological effects in the Prefrontal Cortex (PFC), Amygdala, Hippocampus, Nucleus-Accumbens, Ventral Tegmental Area (VTA), Cerebellum, and Basal Ganglia (Lopez-Moreno et al., 2015). Further research has identified the Cerebral Cortex, Hippocampus, Globus Pallidus, Cerebellum as being the cortical structures where the majority of CB2 receptors are (Pertwee et al., 2010). Functionally NMDR GABBAR and CB1 receptors modulate neurotransmitter production; specifically, the secretion of glutamate, GABA, Serotonin, Dopamine and Acetylcholine within the PFC and Hippocampus, whilst also modulating GABA, Dopamine, and Glutamate in the Amygdala (Huizenga et al. 2019; Ceccarini et al., 2018). Given the range of neurotransmitter systems reliant upon NMDR GABBAR and CB1 functioning, the receptors is a critical component in neuro-pharmacological processes as well as psychological and behavioural functioning (Laaris et al., 2010, Cass et al., 2014). It is logical to conclude, therefore that ethanol and THC from HSD cannabis smoking polydrug exposure would result in deficits to those Psychological and behavioural functions networked through those cortical structures. However, any conclusion made regarding this relationship is tenuous at best as the findings are from rodent and primate studies, as such, it isn't easy to relate these findings to psychological and functional effects of THC upon CB1 functioning in humans (Murphy 2018)

In terms of psychological functioning HSD and cannabis smoking have both been shown to disrupt Long Term Potentiation and Long Term Depression, the neurological process that underpins memory and learning. Psychopharmacological research has shown that the receptor cites affected by ethanol and THC exposure (GABAa, glutamate and CB1 receptors) play a central role in the effective neural communication, which in turn facilitates LTP ad LTD (Bliss and Collingridge, 1993). In this capacity, ethanol can disrupt this process through simultaneous binding to the GABAA receptor of the endogenous inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and inhibition of the function of the excitatory neurotransmitter receiver (NMDR) for glutamate, the primary neurotransmitters necessary for neural communication. By binding to both inhibitory and excitatory receptor cites on pre and postsynaptic neurons. It is reasonable to conclude that ethanol can cause disruption LTP and LTD through suppression of neurological excitation and stimulation of neurological inhibition. (Davis

et al., 2003). The CB1 receptors facilitate LTP and LTD via retrograde signalling of endocannabinoid neurotransmitters from postsynaptic neuron (Xu and He, 2015). Exogenous CB1 agonists such as THC disrupt LTP and LTD induction through binding to the CB1 receptor. This binding action prevents endogenous cannabinoid from functioning correctly. Consequently, suppressing the excitatory neurotransmitter Glutamate and GABA-ergic transmission potentiated (Hu et al., 2013). It is logical to conclude therefor that ethanol and THC induced disruption to LTP potentially affects multiple psychological and behavioural processes.

Upon analysis of the available data on both ethanol and THC's effects on neurotransmission and disruption to LTP and LTD, demographic variables play a significant role in the expression of psychological and behavioural impairment (Broyd et al., 2016, Harvey et al. 2019). Broyd and colleagues were able to demonstrate that age the onset of cannabis misuse is a particularly salient area to consider. This observation was echoed by Broyd, who also noted that the early start of HSD resulted in more significant cognitive impairment when compared to those individuals who began to engage this behaviour later in life. Indeed there seems to be a consensus across cannabis and alcohol literature with regards to the early onset of both drug-taking types and an increase in the severity of cognitive disruption (Connor et al. 2019). The severity of cognitive impairment in both populations is related to the impairment of neurogenesis in the hippocampus and increased stress reactivity (Lee et al., 2014) as well as an impairment to GABA expression in the PFC (Cass et al., 2014). Early exposure to alcohol and THC produces a neuro-inflammatory effect within the PFC (Gao et al. 2019).

It is also important to note that the increase in the availability of affordable alcohol with increased ethanol levels and use of potent strains of cannabis with significantly elevated levels of THC. Combined with the increased prevalence of synthetic cannabinoids such as spice which has a much higher affinity to CB1 receptors raises the possibility of alterations to neurotransmission and alterations to psychological performance (El Sohly et al., 2016, and Thomas et al., 2014). Furthermore, THC's high lipid solubility, its effects on neurotransmission occur within a particular pharmacokinetic context (Ashton, 2001). The body metabolises over 80 to 90% of THC within five days; it can, however, remain in the body of chronic cannabis user up to twenty-four days post-consumption (Lowe et

al., 2009). It recommended that the effects of THC on neurotransmission and attendant psychological functioning are observable within the first five days post-exposure, with a more extended time frame for chronic users.

Polydrug use proposed structural alteration to the brain.

The concerns surrounding toxicity levels raised in the discussion on neurotransmission presented earlier in this chapter are also related to issues of structural alteration—the availability of alcohol with high ethanol content. Strains of cannabis with increased THC levels, as well as synthetic cannabinoids such as spice, which have a higher affinity to the CB1 receptor all, serve to increase potential neurotoxic effects impacting on attendant psychological functioning (Centre for Disease Control, 2011).

Neuroanatomical research has identified discrete regions in the brain that are vulnerable to the effects of both alcohol and cannabis. Referred to as the mesolimbic dopamine system (MLDS) this area includes; the ventral tegmental area, nucleus accumbens, and prefrontal cortex, amygdala, striatum, and Hippocampus (Kalivas and O'Brien 2008 and Spiga et al. 2010). It is logical, therefore, to consider the neuroplastic and attendant neurocognitive changes to these regions.

Research studies conducted by Chanraud et al., (2009) and Campanella et al .,(2013) have noted volumetric reductions to the Fornix and Hippocampus in HSD populations, observed behavioural deficits and damage to hippocampal networked episodic memory. In a recent review examining the effects of cannabis on cortical structural stability, THC, as well as other CB1 agonists, were also associated with structural alterations to the hippocampus. Rodent studies reported that the administration of the synthetic CB1 agonist WIN, 55212-2 was associated with increased cell death and decreased synaptic connections within the PFC when compared to controls. The observed volumetric reductions to these areas result in deficits to psychological and behavioural functions networked through these areas (Bologov et al., 2011). However, it is worth noting that rodent studies have also reported neuroprotective effects in instances of ultra-low doses of THC exposure (Assaf et al., 2011; Fishbein-Kaminietsky et al., 2014). In an attempt to explain this differential in effect, mechanisms reflecting the internal state of the cell and

its innate viability have been proposed, with weaker natural states serving to enhance vulnerability to neurotoxicity (Bologov et al. 2011).

Studies conducted in groups with uncomplicated alcoholism have identified compromised white matter in the temporal lobe (Gazdzinski et al., 2005) and microstructural grey matter abnormalities in the hippocampal formation (Chanraud et al., 2009). Volumetric reductions in Grey Matter concentrations within the Hippocampus of Cannabis users have observed in recent neuroimaging reviews by Lorrenzetti et al. (2016) and Rocchetti et al. (2013). In both studies, exclusion criteria included a diagnosis of Psychosis, thus removing any potential methodological confounds as a result of neuroanatomical alterations typified by these conditions. Results from the Meta-Analytic review conducted by Rocchettie and colleagues found statistically significant volumetric reductions to overall hippocampal volume. The author concluded that since the hippocampus is a critical cortical structure implicated in memory task performance, volumetric reductions to this structure serves to highlight the potential role of exogenous cannabinoids in declines in memory and learning.

Battistella et al. (2014) were able to validate the notion that there does indeed exist a relationship between cannabis use Hippocampal volume reductions. Results from Battistella and colleagues indicated that cannabis use from under eighteen years of age was associated with a significant reduction in grey matter in the left Para Hippocampal Gyrus between the ages of nineteen and twenty-nine when compared to the onset of cannabis use after the age of eighteen. Misuse levels also were associated with Hippocampus changes. Persistent cannabis misuse resulted in statistically significant reductions in grey matter concentrations when compared to recreational users. However, the study failed to find the duration of use to be a reliable moderator for this effect. However, this result may be due to the insensitive nature of the analysis of cannabis consumption by the participants. It is also worth noting that insufficient data reporting on consumption meant that this as a viable moderation in the Meta-Regression. There were also conflicting reports for the primary studies cited in this review, Ashtari et al., (2011) reported a negative correlation between Hippocampal volume in the gyrus and estimates of the number of cannabis cigarettes smoked while Tizolis et al. (2005) reported no relationship.

Evidence from within the literature also suggests that exogenous cannabinoids play a significant role in the impairment of emotion and memory with reported reductions to the functional connections between the hippocampus, amygdala, and cortical structures implicated in emotion processing (Lorenzetti et al., 2016). Lorenzetti and colleagues reported reductions in amygdala volume in cannabis users when compared to controls, with additional studies highlighting an increased grey matter density and alterations to amygdala morphology.

Research investigating the PFC have reported cortical density alterations related to the age of cannabis use onset. Studies have demonstrated that cannabis consumption negatively correlates with the age of onset use and density to the right superior frontal lobe. Urine analysis reported a negative correlation to cannabis consumption levels and the thickness of the cadual middle of the right frontal lobe, right lingual and left superior gyrus. The author concluded that there seems to be a relationship between structural alterations to those areas of the brain and cannabis users compared to controls. Synaptic connectivity in these regions also plays a potential role in the development of structural changes related to cannabis consumption (Lorenzetti et al., 2016). In a review by Chanraud et al. (2009), HSD resulted in grey matter shrinkage of the frontal lobes, pons, thalamus and cerebellum. Moreover, through the use of tractography, research has shown decreased white matter density between the PFC midbrain and the pons in HSD populations.

The potential impact of nicotine on polydrug use

Evidence from within the broader academic literature has noted that nicotine consumption in the form of cigarette smoking is prevalent in HSD and Cannabis consumption research, (Herschberger et al. 2020). The EMCDDA (2019) notes that nicotine usage in both binge drinking and cannabis consuming populations is considerably higher than the rest of the community. Statistics notes that nicotine use amongst the general population is approximately 15%, but that this rises to 40% in binge drinkers and 75% in cannabis users. Neuropsychological research has demonstrated that nicotine consumption results

in deficits to WM and EF. It is logical, therefore, to consider the impact of nicotine use with regards to binge drinking and cannabis smoking polydrug use.

While the neurotoxic properties of nicotine are yet to be clarified, the existing studies report similar patterns of cortical damage as that observed in HSD and cannabis consumption. Specifically, lower grey matter density in the prefrontal cortex, cingulate gyrus, parietal lobe, cerebellum, thalamus, striatum and medial temporal lobe. HSD cannabis and nicotine misuse have also resulted in deficits in working memory and executive functions. (Jacobsen et al. 2007, Musso, et al. 2007).

Research conducted by Nardone et al. (2020) reported that nicotine use was positively correlated with deficits to WM and EF in cannabis smokers. Results indicated that participants displayed deficits to spatial working memory on the delayed response task. The researchers concluded that damage to delayed response is indicative of impairment in the DLPFC. Otto et al. (2020) reported that combinations of ethanol and nicotine resulted in decreased visuospatial working memory task performance. The research assessed participants with regards to the Corsi block tapping test, those individuals who reported co-usage of nicotine had visible deficits to the total number of blocks remembers and overall reaction time.

Neuropsychological research has observed that nicotine, ethanol, and THC alter nicotinic-acetyl cholinergic receptor response. Studies reported similar withdrawal responses in HSD, cannabis and nicotine misuse. The authors suggested that this is indicative of similar functional and biochemical interactions taking place between the three substances. From the evidence within the broader academic literature, there does appear to be convergent evidence to suggest that nicotine has additional consequences for WM and EF impairment (Valjent et al. 2002). However, to date, the precise neuroanatomical effects of nicotine use are not precisely known, nor are the interactions between HSD and cannabis combination (Gonzales et al. 2020).

Given the evidence presented it logical to conclude that any investigation into binge drinking and cannabis consumption must factor in the potential effect that nicotine consumption can have to both WM and EF task performance

Conclusion

In conclusion, from the evidence presented, both heavy social drinking and cannabis consumption properties neurotoxic properties. Both substances act as a depressant on the CNS and disrupt regular neural communication and long-term potentiation. The act of binge drinking cannabis smoking polydrug could potentially have a cumulative effect on neurological integrity and would show more significant impairment than single drug users.

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Chapter 2:

Heavy Social Drinking cannabis smoking polydrug use. Bio-Psychological implications for memory, learning and behaviour

Verbal Learning and Memory

Reviews into the constructs Verbal Learning and Memory have demonstrated that these are cognitive domains in which primary studies have been able to establish impaired functioning in both HSD and cannabis smoking populations when compared to controls. In addition to this, research has also been able to demonstrate a correlational relationship between the estimates of lifetime substance misuse and task performance (Broyd et al. 2016 & Jones et al.,2019).

Research findings from Solowji et al. (2011) based on a sample of adolescent cannabis users, assessed using the Rey Auditory Verbal-Learning Test (RAVALT) demonstrate deficits in word recall, verbal learning, retention and retrieval when compared to non-cannabis smoking controls. Upon a more detailed consideration of the findings, the results indicated that cannabis consumption resulted in measurable deficits to a total of eight out of eleven key performance indicators. In HSD research, Parada et al. (2011) reported that HSD displayed significant reductions in word recall and greater interference to word recall when compared to controls. In both of these studies, the researchers were able to observe a correlational relationship between deficits in task performance and estimated lifetime substance misuse, whereby higher quantities and frequency of use resulted in increased impairment. Results also indicated that in both the HSD and cannabis studies, the average age of onset was a significant factor in verbal learning memory task performance. With intoxication as a potential methodological confound, both studies made use of a washout period, twelve hours for Solowji and colleagues.

In comparison, Parada employed a washout period of twenty-four hours. Also, there was a median abstinence period for participation in Solowji and colleagues research, with the cannabis users having to display abstinence of twenty point three hours. However, no additional abstinence criteria, other than the one day washout period, was recorded in the HSD group. In Solowji's research, a urinary analysis employed to control for the presence of cannabinoid metabolites. However, there was no observable relationship from the other

four measures. With no indication of toxicological screening in Parada's research, it is impossible to comment on the impact that alcohol's presence may have played on task performance.

Bolla et al. (2002) were able to demonstrate, that when comparing neuropsychological performance to cannabis consumption, a negative correlation existed between consumption level and deficits to delayed recall on the RAVALT following twenty-eight-day abstinence. However, it is worth noting that Bolla and colleagues did not use a control group to compare their results. Similarly, concerning HSD Cabria et al. (2017) also reported a negative correlation between two of the conditions on the RAVALT decreases in immediate recall and delayed recall of stores and length of time engaged in HSD.

In a study conducted by Medina et al. (2007) cannabis users performed significantly worse than non-cannabis smoking controls on verbal story memory when analysed using the Wechsler's Memory Scale version three (WMS III). Groth et al. (2018), in direct response to the research conducted by Cabria et al. (2017) noted that the observed deficits verbal learning where validated on a more extended battery of tests, with participant's performing worse on recognition ability, on the California Verbal Learning Test (CVLT). The study failed to find a significant gender difference, although years of alcohol misuse and task performance were weakly correlated. Similarly, Medina and colleagues were unable to find a connection between cannabis consumption and verbal list learning when using the California Verbal List Test (CVLT). Cannabis consumption was, however, associated with deficits to intricate attention when within a non-verbal learning task. Correlational analysis indicated that scores of verbal story memory and detailed attention is related to increased estimates of lifetime use.

Therefore, there does appear to be a relationship between HSD, cannabis consumption and deficits to learning ability and memory. Correlational analysis indicates that increased levels of either alcohol or cannabis are related to decreases in task performance, and age of onset also appears to play a significant role, with the highest levels of deficits being present in those who have engaged in the behaviours for an extended period. Given the array of evidence from primary studies presented within this review, these observations

appear to be the accepted consensus within the academic literature. It is logical to assume therefore that any investigation into HSD Cannabis smoking polydrug use would show that polydrug users would display elevated levels of impairment to learning and memory when compared to users of either substance separately or controls.

Working Memory

A different domain that impaired in both HSD and cannabis smokers is that of Working Memory (WM). Unlike verbal learning and memory, however, WM is a field of research where primary studies have been unable to establish a consensus with regards to substance misuse and task performance. Generally speaking, this is because WM covers a broad range of domains such as visual or auditory memory information processing (Murphy et al. 2018). This particular cognitive construct also involves aspects of executive control (which will be described later on in this review) in the form of decision making (Baddley, 2000, Miyakee, 1999). Indeed, Murphy et al. (2018) note that through Latent Variable Analysis, it is clear that the Visuo-Spatial aspect of WM is relying heavily upon executive functions. This processing is not contingent upon any higher order level of processing beyond the acquisition and storage of the information (Miyake et al., 2001).

Consequently, given the range of executive processes concerning WM and the plethora of potential stimuli available (Fisk & Sharp 2004, Miyakee et al., 2000). A point of particular concern within the field of substance misuse, was the variety of neuropsychological measures employed by research teams is one of the primary factors implicated in the contradictory sets of results often observed when discussing WM impairment concerning both HSD and cannabis consumption (Broyd et al. 2016). The lack of consistency across research studies about the WM tasks employed is in part responsible for a general lack of clarity regarding substance misuse and WM impairment. Broyd and colleagues note that the one exception to this observation is those studies that have investigated WM impairment following exposure to the synthetic cannabinoids.

Despite the methodological issues around accurately assessing WM task performance and substance misuse, evidence from within the psychological literature that has been able to demonstrate the N-back test is a reliable WM tool for establishing relationships between

substance misuse and impairments to WM performance (Jaeggi et al. 2010). In support of this argument, Cousjin et al. (2014) study examining the effects of cannabis consumption on WM using the N-Back indicated that cannabis users displayed significant deficits to WM when assessed on the N-Back test. Harvey et al. (2007) were able to report spatial WM deficits in cannabis users when analysing them using the Cambridge Neuropsychological Automated Test Battery (CANTAB). Whilst the abstinence period of this test, that of twelve hours, is within the accepted limits, the relative age of the participants (thirteen to eighteen) is considerably younger than the average for this type of research (eighteen to thirty). The two studies by Cousjin also contained neuroimaging elements to them. They were able to report observable differences in cortical activation patterns in the DLPFC with letters as a stimulus. Indeed the N-Back has been sown to be a consistent measure for the assessment of HSD induced WM impairment, Mahedy et al. (2018) was able to demonstrate that HSD displayed more significant impairment to WM on a 3 Back condition when compared to controls. Neuroimaging research by Park and Kim (2018) has been able to demonstrate that HSD affects attendant neurological impairment. The researchers reported that while no significant difference in a 2-Back condition was initially present with controls HSD's displayed greater neurological exertion to maintain a relative level of task performance to the control group, which is indicative of impaired functioning to WM in the HSD condition.

Whilst investigations into WM and substance misuse has found some level of consistency with the use of the N-Back. Contradictory sets of results serve to highlight the fact that 'these conclusions are tenuous at best and prevent any firm conclusions. Findings presented by Smith et al. (2006), in a longitudinal study assessing Visuo-Spatial Working memory consistently failed to find any significant difference between controls and cannabis users over twenty years. Veredejo-Garcia et al. (2015) also reported that no significant effect for any of the 3 N Back conditions where a visual stimulus (a circle) with spatial positions used as the determinant factor. In this study, the washout period was seventy-two hours, and medication alleviated any withdrawal effects. Whilst Squeglia et al. (2011) was only able to find a partial relationship between WM impairment concerning HSD. Specifically, Squeglia and colleagues found females reported deficits to WM, while males were displaying no such impairments to task performance, Verdejo-Garcia and Herzig failed to account for other drug misuses in any substantive detail. Indeed this is as a significant methodological confound, other studies (Montgomery &

Fisk, 2008; Wareing et al., 2004) have failed to demonstrate any relationship between spatial memory which also took Ecstasy (MDMA).

Concerning any study considering the misuse of cannabis, Cohen (2017) notes that it is worth discussing the reported increase in the use of synthetic cannabinoids. Cohen has been able to demonstrate a consistent deficit in WM task performance on the N-Back test, precisely the 2 Back condition when digits are a stimulus. When measuring the inhibitory aspects of WM via the Stroop Test results have also yielded significant levels of impairment in cannabis smoking populations, (Miyakee et al.,.2006). The potent agonistic effects of these cannabinoid strains and their apparent effects on WM performance make them an important target for future research looking into substance-induced deficits to WM, (CDC & Prevention., 2013; Thomas et al. 2014).

The literature examining the effects of HSD and cannabis consumption on WM performance is not consistent in their finding's when compared to investigations into learning and memory. Difficulties in operationalising these investigations and potential methodological confounds which are interfering with results. Tests such as the N-Back are more robust at providing consistent findings and given the prevalence synthetic cannabinoids with high CB1 affinities (as discussed in chapter 1, discussion of WM impairment in polydrug research is still of vital importance.

Executive Functioning

As discussed earlier within this chapter, executive functions (EF) are constructs that load heavily onto working memory (Baddley, 2000, Miyakee et al., 2000). However, EF can also refer to a much broader set of cognitive tools centred around problem-solving, planning and decision making. Within the scientific literature, these are; Task Switching, Inhibitory control, and executive updating. As with WM examination of the effects of HSD and cannabis, smoking on EF is within the substance misuse literature. As with WM, studies within this field often report conflicting results. Broyd et al. (2016) concluded that the mixed findings often cited within the literature can be related to methodological limitations within individual research studies. Such as not accounting for prior exposure to cannabis before testing, the dosage of THC consumed, or for haematological

concentrations of THC still present within the body (Lezak et al., 2012, Yuen & Raz., 2014).

One test of EF that has been able to demonstrate consistent results across studies in both HSD and cannabis smoking populations is that of the Iowa Gambling Task (IGT). Bechara et al. (1994) summarise the task conditions; participants are required to try and make as much money as possible by selecting cards from four decks. In two of the decks, there is the possibility of increased gains. However, the possibility of losing all the accumulated money is high, in the other two decks of cards, the returns are comparatively low, and yet, the chances of losing the capital are equally minor. Moreno et al. 2012 and were able to demonstrate that both cannabis smokers and HSD consistently displayed impaired performance on this task when compared to controls when participants had to be abstinent form either substance for three days before testing. Gonzalez et al., (2012, 2015) and Parks et al. (2018) were able to report that in instances where substance misuse did not appear to play a role in task performance. When the IGT was the measure of EF, a more detailed analysis of the results concerning relevant demographic variables was indeed able to produce statistically significant differences between HDS and cannabis smokers when compared to controls. Gonzales and colleagues were able to identify lower task performance on the IGT related to substance dependency symptoms and personal issues arising from substance misuse. Maurage and colleagues reported no difference between HSD and controls on the IGT. There was a significant difference when the test included a real-world monetary risk, and in those instances, HSD reported significant deficits to decision making when compared to controls.

As with Working Memory, whilst a pattern of disruption to Executive Functioning performance in both populations is evident, these conclusions are again tenuous as studies have also reported no relationship. Research conducted by Veredejo-Garcia et al. (2015) reported an inverse correlation between THC levels and cognitive flexibility. No significant differences in comparison to controls were observed in the assessment of task inhibition whilst using the Stroop Task. Whilst Gill-Hernandez et al. (2017) found that in a study of three hundred and twenty-two students aged between thirteen and twenty-two when compared in terms of EF performance, the researchers did not find a difference between the two groups. Additionally. The researchers were unable to find a correlational

relationship between the average number of units consumed and alterations to EF performance. However, the researchers do admit that that maturational development may serve as a neuroprotective agent.

One significant limitation of the investigations into EF performance and substance misuse is the issue of ecological validity of the task employed, so that the contradictory set of results may be the result of the tests used (Wallisch et al. 2018). Montgomery et al. (2012) attempted to address this issue by requiring participants to engage in a Virtual Reality (VR) task which loaded onto EF processes. The test required participants to engage in tests in a simulation of an office environment. Results indicated that cannabis users displayed significant impairment in planning performance, yet no difference to adaptive or creative thinking.

It is logical to conclude therefore that as with WM, the broad range of cognitive skills that can are EF and the comparatively broad array of tests that can be employed to this domain make it difficult to draw any conclusions. At the same time, researches such as Boyd et al. (2016) and Gill-Hernandez (2017) note that the length of substance misuse in both HSD and cannabis smoking populations is a significant confounding variable. Issue of age-related decline in mental functioning is a further issue that has to be taken into account when interoperating these results.

Psychobiological implications for behavioural deficits.

The cognitive impairment observed in both HSD and cannabis smoking populations does not sit within a vacuum, independent from behavioural phenomena. Instead, the deficits to both WM and EF may actively contribute to the development and maintenance of maladaptive behavioural traits and, therefore, suggest some tentative conclusions about the possible behavioural deficits in HDS cannabis smoking polydrug users (Cohen et al. 2017).

In addition to WM and EF, the pharmacological consequence of HSD and Cannabis consumption contribute to behavioural issues (Goudriaan et al ., 2005; Le Berre et al .,

2012; Noël et al ., 2007). Behavioural research has shown that binge drinkers and cannabis smokers both favour the instant gratification of using either substance. They will tend to ignore its long-term negative consequences; this supports the argument that both populations share a disability within their decision making capability (Goudriaan et al ., 2005).

Neuro-anatomical research around the concept of the somatic marker theory suggests that decision making involves an extended brain network, controlled through a dual neural circuitry pathway: the impulsive and reflective systems. The model suggests that during the development of a substance misuse pattern of behaviour, the impulsivity system, via the amygdala, triggers a somatic state from stimuli (emotion, alcohol and cannabis) present in the immediate environment. The behaviours of those binge drinkers and cannabis smokers become increasingly influenced by alcohol and cannabis-related stimuli. These stimuli develop the ability to elicit both cravings for and motivation to engage in binge drinking and cannabis smoking behaviours. Persistent engagement in these behaviours leads to a strengthening of implicit desire. Relevant associative memories can, therefore, generate automatic approach tendencies (Stacy and Wiers, 2010). The impulsive system, in turn, is linked to the reflective system this allows for a more flexible pursuit of long-term goals). Anatomically speaking the reflective system is networked through two neural networks referred to as both “hot and cold” executive functioning system. The terms hot and cold with executive functions notes a movement away from a purely cognitive conceptualisation of executive functioning to one which emphasises the motivational significance of the situation the executive functions are related. “Cold” executive functions (those evoked under abstract non-affective conditions) in the the “Fronto-cerebellar circuit (Zahr et al., 2010). Hot cognitive (motivationally significant) networked in the paralimbic and otbitomedial structures (Bechara et al. 2005). Thus, the neurological pathway employed is a function of the emotional significance the individual places upon the situation in which the executive functions are used (Zelazo and Muller 2002). Arguably, everyday decision-making requires the integration of “hot and cold” systems and the ability to consider short- and long-term gains or losses (Beaunieux et al., 2014).

Research indicates that the somatic marker brain network that is susceptible to the neurotoxic effects of alcohol and cannabis. The frontal cortices, amygdala, hippocampus, striatum and cerebellum are particularly vulnerable to the neurotoxic effects of alcohol and cannabis. Le Berre et al. (2012) reported that reductions in both white and grey matter volume in specific frontal lobe regions result in decision making deficits. Hanlon (2016) and Veredejo-García, (2008) noted a volumetric decrease in the frontal and parietal lobes, and reductions in the grey matter fibres are associated with a decrease in information encoding during visual decision-making tasks. These results suggest that decision-making deficits in the substance misuse group may result from impairment of frontal lobe networks. Behaviourally these deficits could lead polydrug users to a more significant "myopia" for the future, this would then motivate them to choose instant gratification to a greater extent than single drug users (i.e., the immediate advantages of their alcohol and cannabis consumption). This "myopia" may inhibit the polydrug users' ability to fully comprehend the long term consequences of this form of substance misuse. It would, therefore, hinder their ability to seek treatment for their behaviours (Verdejo-García 2015).

Both HSD and cannabis smoking populations display addiction and dependency personality traits that have attributed to the abuse of both substances (Blum 2012 & Hathaway 2004). According to Segal (2010), the categories of cannabis misuse are; Cannabis Use Disorder (CUD), Cannabis Intoxication (CI), Cannabis Withdrawal (CW) (CID) and (UCRD), with these traits related to the activation of the dopaminergic neurons within the Ventral Tegmental Area (VTA). The Substantia Nigra, is also implicated in the behavioural reward pathways within the brain (Clapp et al. 2008). The VTA has strong connections to the Nucleus Acumbens, activation of which has reinforcements substance misuse behaviours (Filbey et al. 2009). This neurological foundation helps to elucidate the biomechanical mechanisms by which perpetuate substance misuse. In short, the release of dopamine following these substance taking behaviours acts as positive reinforcement, so that individuals repeatedly engage in these behaviours (Murphy et al. 2018).

Both HSD and cannabis consumption can also encourage the engagement in drug-seeking behaviour through serving as a negative reinforce as a means of avoiding the negative

physiological consequences of substance withdrawal (Barker et al. 2004). According to the Diagnostic Statistical Manual, Version Five (DSM V), three or more of the following behavioural criteria need to meet the conditions for a diagnosis of substance withdrawal. Behavioural changes, following the cessation of prolonged substance misuse (this includes but is not mutually exclusive to HSD and cannabis smoking). Irritability, anger, anxiety, sleep deficits, decrease in appetite, weight loss, restlessness, depressed mood (APA 2013, p518). These characteristics occur in research settings, with Kerridge et al. (2018) being able to elicit the DSM V characteristics of Cannabis withdrawal syndrome in participants two days after the onset of abstinence.

The DSM V is the first iteration of the manual to include Cannabis Withdrawal Syndrome as a diagnosable condition. Murphy (2018) attributes this change to wider recognition by clinicians and politicians to the threat to public wellbeing posed by the newer strains of cannabis with increased levels to THC and the increased prevalence of artificial Cannabinoids with a higher affinity to CB1 receptors as discussed in chapter 1. Given the synergistic effect of cannabis and alcohol and neural communication, cortical structural abnormalities, and attendant learning, WM, EF and behavioural characteristics. HSD cannabis smoking polydrug use is a crucial area of research as the alterations to cannabis, and the artificial strains could cause increased damage to these areas compared to traditional types.

The relevance of other baselines in polydrug research

One salient issue with regards to polydrug use is the correct identification of control group selection criteria. It is the nature of the control group, which constitutes the baseline against which research will use to compare the effects in drug-using groups in polydrug use. Consequently, the nature of the control group is of fundamental importance in the interpretation of results obtained. To date, there is no consensus on the appropriate inclusion criteria for control groups in polydrug research. The failure to establish an agreement on proper inclusion protocols is likely to contribute to the indeterminate nature of WM and EF findings in polydrug research (Singh et al., 2020). Control groups tend towards one of two different types, the drug naïve control (Taylor, 2020.) and a single drug using control group (Toegel et al., 2020.). Research has used both of these group typed to good effect.

Taurah et al. (2014) investigated the effects of ecstasy polydrug on WM and compared scores with four control groups, one a drug naïve, the other alcohol and nicotine, alcohol, cannabis and nicotine and a non-ecstasy polydrug group. However, operationalising such a study would present methodological problems, notably, to have statistical significance, such tasks required inflated population samples. The current research the total population size was (N = 997) Similarly, Kelly et al. (2017) investigated the effects of cocaine and amphetamine polydrug use against a drug naïve control group. Results indicated that the polydrug use results in significantly more impairment on measures of WM. However, the author did concede that the failure to include amphetamine and cocaine only controls limited the scope of the conclusions. Specifically, there was no way to know to what extent each substance contributed to the impairment.

Given the potential for greater clarity of results, it would be logical to conclude that the use of single substance controls should be the standard for all polydrug research. However, Kataja et al. (2017) note that it is often challenging to recruit individuals who use only one type of drug. The attendant psychological variables that help to determine drug-taking behaviour predisposition, namely impulsivity, actively contributes to the use of multiple drug types. Therefore, while the use of single drug using controls would represent a gold standard in this type of research, methodological difficulties around participant recruitment require a degree of flexibility in this regard.

Issues around the interpretation of results and methodological limitations

As in any investigation into substance misuse, analysis of the effects of HSD and cannabis require recruitment from populations of individuals regularly engage in these behaviours. It is difficult to develop adequate washout periods owing to THC's presence in the systems of heavy users, its action upon dopaminergic systems, and the effects of withdrawal (Bundy et al., 2004). Furthermore, the aetiology of withdrawal of either of these substances includes sleep disturbances. A potential methodological confound as sleep deprivation impact upon EF and WM task performance. Lowe et al. (2009) who notes that as urinary analysis has suggested that while alcohol metabolises after several hours even in individuals who engage in extreme binge drinking THC is present in the bodies of chronic users for over twenty-three days.

Given that the majority of studies employ a washout period a month, this means results from these studies are susceptible to the detection of neurological impairment as a function of exogenous cannabinoid toxicity rather than the detection of any latent long terms effects. Addressing this issue, therefore, requires a degree of pragmatism on the part of the researcher. Murphy (2018) offers a solution to this issue by applying a standardised twenty-four-hour washout level with mean abstinence levels also being reported.

A further issue with regards to testing of participants within HSD and cannabis misuse research is that of the adequate identification and control for known confounding variables. Traditionally within the scientific literature, relationships between variables are analysed through random allocation to either an experimental or control condition, to assess the correlational relationship between the identified independent and dependent variables. Participants wishing to take part in studies examining either HSD or cannabis consumption and cognitive processes would have to be assigned randomly to either condition. The experimental group, exposed to HSD drinking levels of alcohol and cannabis, would impracticable and violates the ethical codes of conduct for human testing. Therefore substance misuse research takes an a priori approach to screen and control for all known confounding variables that can impact upon cognitive performance (Valls-Serrano et al., 2016). Therefore, the prescriptive nature of substance misuse research means that experiments into HSD and cannabis smoking are correlational so that relationships can be demonstrable when a difference in task performance between the groups. However causal relationships remain a significant issue, raising issues around the utility of research in this field

Conclusion

From the evidence presented, there is a significant degree of overlap in the psychobiological consequences of both HSD and cannabis consumption. Their effects, with regards to WM, EF, and attendant behavioural impairments, provide a basis for understanding the possible consequences of HSD cannabis smoking polydrug use. However, it is evident from the research already within the academic literature that

existing issues around the ethical and methodological limitations of research with human participants preclude any confirm cause and effect conclusions from being drawn. The results from these studies do still provide a basis for concern regarding the impact of polydrug use on cognitive and behavioural performance. This concern is enhanced when considering the increasing prevalence of strains of cannabis with artificially elevated levels of THC and the emergence of synthetic cannabinoids shown to have a higher affinity to the CB1 receptor. The issue of understanding the consequences of HSD cannabis polydrug use, therefore, can be seen as one of addressing an ever-increasing public health concern. Research into this field can potentially serve as a basis for the formulation of effective substance misuse interventions. It is worth noting, however, that those arguments made in this, and chapter one is based on the reading of work from other research teams and drawing conclusions from what they report. Therefore, the next step in addressing this issue is to calculate results around working memory impairment with alcohol and cannabis consumption. Thus, the thesis will identify weather a precedent for the assertion made exists within academic literature through the use of meta-analytic techniques.

Chapter 3

Visuospatial Performance in Binge Drinkers who Smoke Cannabis, Literature review and Meta-Analysis

Introduction

Chapter 2 discusses the effects of binge drinking and cannabis smoking combinations on executive functioning task performance more broadly. However, a scoping search of the academic literature (as described in the Methods section of this chapter) notes that one of the most widely researched EF domains with regards to binge drinking, and cannabis smoking research is that of Visuospatial working memory task performance.

The Visual and spatial aspects of working memory, more broadly referred to as Visuospatial working memory, is assumed to hold and process information related to visual stimuli. The temporary storage and manipulation of spatial and visual information, such as remembering shapes and colours, or the location or speed of objects in space. It is also involved in tasks which include planning of spatial movements, like planning one's way through a complex building (Baddley 2003)

Visuospatial working memory is divided into separate visual, spatial and possibly kinaesthetic (movement) components. Specifically, Logie (1995) proposed that a multi-component perspective suggests that modality-specific subsystems control the different aspects of Visuospatial processing. Logie (2003) indicated that the Visuospatial subsystem is two distinct components: An optical storage component (the inner Scribe) and a more dynamic spatial rehearsal component were both proposed to exist (Visual Cache). Whereas the visual element is sensitive to decay and interference, the spatial rehearsal mechanism actively refreshes the contents of the store and helps to retain spatial, sequential information. It also rehearses stimuli in the visual cache and transfers data to the central executive (Logie 1995).

As discussed in chapter two, research within the academic literature has found that consumption of binging levels of alcohol has resulted in visuospatial working memory deficits, for example. Kokavec & Crowe (1999) identified observable differences in task

performance. In conjunction with these Working Memory tasks, the study investigated executive functioning results for both groups, and binge drinkers displayed more significant dysfunction than non-binge drinkers on memory tasks.

Research has also reported deficits to visuospatial working memory in cannabis smoking populations. For example, Meyerhoff et al. (2004) reported a causal relationship between levels of cannabis consumed and VSWM task scores. Correlation analysis indicated that as THC units increased cognitive performance decreased, with lowest scores on executive functioning and VSWM, reductions in grey and white matter were also observed in the frontal lobe associated with impaired executive functioning and processing speed. The results imply that cannabis smoking results in a reduction in parietal neurons when compared to non-smoking controls and that THC exposure may result in relatively specific neural deficits.

However, there is no consensus on this issue within the academic literature, with a significant body of research also indicating no significant effect for visuospatial working memory impairment for either binge drinking or cannabis smoking populations. For example, in a meta-analysis conducted by Calabria et al. (2018), the author reported that the current consensus with regards to binge drinking induced working memory defects is that this form of substance misuse has no negative impact upon Working Memory task performance. In cannabis consumption research, meta-analytic results reported by Crean et al., (2011) said that although the studies conducted into cannabis and working memory are limited, the available evidence emphasises the indeterminate nature of the research in the field today. The author notes that out of the four studies that investigated this aspect of working memory, three found no significant difference between cannabis users and controls.

Animal model studies may provide one potential explanation for the indeterminate nature of the results presented in the literature. However, there is a consensus within the academic literature about the requirement for rat and primate studies into both binge drinking and cannabis smoking to provide long-term (over months) exposure to begin to elicit a behavioural effect (Wezeman, Juknelis, Himes, & Callaci, 2007). Given that most

of the human studies reported are on undergraduate populations, the authors conclude that animal studies have not provided sufficiently long exposure to substances for an observable behavioural effect to become detectable. Advances in the field of imaging technology have afforded researchers access to a broader array of techniques that could potentially account for the indeterminate nature of results found thus far (Casey et al., 2005). Introduction of these approaches to the field of substance misuse has been able to provide researchers with evidence of physiological damage caused by both THC and ethanol, even when no apparent behavioural impairment is evident (Dickerson et al., 2007).

Using imaging techniques such as Magnetic Resonance Imaging (MRI) research has been able to demonstrate that THC and ethanol also cause physiological damage to the cortical structures in VSWM in humans. For example, Meyerhoff et al., (2004) measured cortical white and grey matter regional volumes to quantify N-acetylaspartate (NAA) concentrations (a metabolite biomarker of neural integrity). For bingers (> 100/80 alcohol drinks/month on <21 days in the past three years) compared with non-bingers, results indicated a significant reduction in NAA concentrations, which, in turn, increased the metabolic rate and frontal white matter density reduction, with higher parietal grey matter NAA. Studies state that both THC and ethanol exposure both lead to neurodegeneration in corticolimbic areas (Haberly, 1998). The research found that ethanol and THC exposure results in neurodegeneration that produced learning deficits (Obernier, White, Swartzwelder, & Crews, 2002). Neuroimaging technology has implicated cannabis consumption to prefrontal cortex damage during visuospatial task performance. For example, Jagger et al. (2006) reported that the binge drinkers displayed comparable task performance scores to the control group during the working memory task and the selective attention task. At the same time, preliminary neuroimaging results indicated that binge drinkers did not differ from controls in terms of overall patterns of brain activity in the regions involved in these cognitive functions. A more detailed analysis of prefrontal cortex structures indicted that the binge drinkers displayed a significant alteration in brain activity in the left superior parietal cortex.

It is logical to conclude from the evidence presented thus far that binge drinking, and cannabis consumption combinations have the potential to affect behavioural task

performance for executive functions such as visuospatial working memory networked within DLPFC cortical structures. Consequently, binge drinking and cannabis smoking could theoretically impair VSWM task performance in several ways involving a range of neural locations within the prefrontal cortex and DLPFC for the processing of different aspects of VSWM (Weise et al., 2019).

This present study uses systematic review and meta-analytic methodology in a preliminary investigation of the respective relationships between combined cannabis and alcohol consumption, and visuospatial working memory task performance.

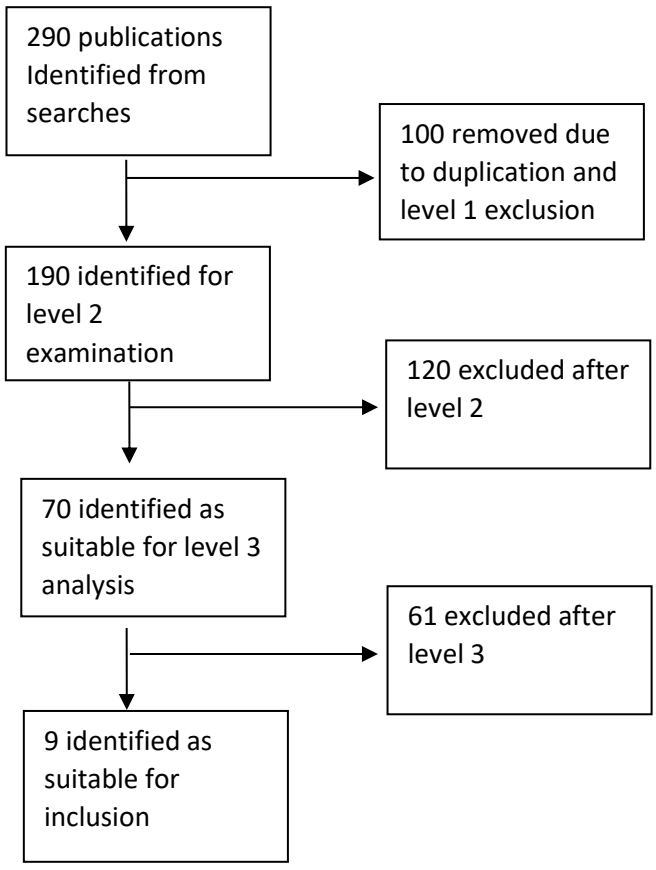
Methods

Identification of studies

A preliminary search of literature covering the period up to June 2019 identified publications relating to the effects of binge drinking and cannabis consumption on visuospatial performance in humans. The analysis searched the PsycInfo, Pubmed, cinall and Web of Science databases. Searching criteria used eight terms in which the search parameters paired either 'binge drinking', cannabis, and polydrug with 'spatial', 'visual', 'Visuospatial' or 'visuospatial'. All databases avoided duplication. The search employed the following keywords and their corresponding synonyms: Binge drinking, cannabis, visual, visuospatial or Visuospatial, spatial and performance. In this second search, it was possible to explore these terms utilising the relevant database thesaurus to ensure completeness of data. Inclusion criteria included English language publications with human participants. Other measures were that studies had to be in peer-reviewed journals and to be reporting new findings (including attempted replications) regarding visuospatial memory performance in the context of binge drinking and cannabis use. Participants needed to have been abstinent from cannabis, alcohol and other drugs of misuse at the time of testing. By implication, therefore, this review excluded studies that tested participants under the influence of alcohol, cannabis or other drug, animal studies and studies published in a language other than English, as well as dissertations, conference presentations, reviews or meta-analyses. Inclusion in the review sample did not automatically imply inclusion in meta-analyses, as additional criteria regarding study design, tasks employed and the reporting of data were relevant to these decisions and are in the Analytic Strategy section.

Figure 1 outlines the search process and corresponding inclusion and exclusion criteria for this study. The term 'publication' emphasised the diversity of items initially identified. Level 1 examination against the inclusion/exclusion criteria excluded papers where, for example, the search terms' binge drinking' and 'spatial', resulted in the identification of publications from the realms of the creative arts and engineering. The study also removed duplications of research papers at this stage. The study identified two levels of examination against the inclusion/exclusion criteria for the remaining 190 reviews. These two levels may differentiate the extent of analysis required. For example, in some cases, it was possible to identify animal studies and reviews from their abstracts and a preliminary examination of the main text. A Level 2 examination against the inclusion/exclusion criteria. The studies examined the 70 studies identified as receiving a Level 3 examination against the inclusion/exclusion criteria in detail to assess their compatibility with these criteria. Table 2 summarises the points of the studies included in the review

Figure 1: Mapping of the literature search process.



Data extraction

For each research paper included in the review, the study recorded the details for each subgroup of participants regarding estimated cannabis and alcohol consumption for the last three months, and the number of participants included in each analysis and subgroup. The study also reported the types of visuospatial task employed and corresponding means and standard deviations. These variables in their published form took the forms of means and standard deviations. Where Papers did not record average, the mean alcoholic units and cannabis joints smoked in the last three months; calculations were made of an implied estimate, if possible, from the available data. Where researchers had explicitly intended to compare the performance of cannabis and binge drinkers with the control group, the study regarded the former as the experimental groups unless the study did expressly stated otherwise. However, the study detailed the use of cannabis and alcohol enough to indicate either binging or non-binging behaviours so that it was possible to identify the participants as belonging to either a control or an experimental group. The study did not require that the use of any other illicit substance, other than cannabis, had resulted in the exclusion of participants in the primary studies constituting the present sample. Minor infringements of the inclusion criteria were permitted by the author, for example, in the case of Smith et al. (2010). The researchers enabled participants with a low level of lifetime cannabis exposure into the drug-naive control groups. In this sample of studies; there was a general trend of allowing individuals inclusion into a drug-naive control group who displayed long term exposure to legally available substances such as tobacco, i.e. Grant et al. (2012). However, all participants had been abstinent from cannabis and other illegal drugs at the time of testing, and the study did not include groups designated as former users. Given the evidence that compromised brain functioning may return to levels consistent with that of controls in former users (Buchert et al.,2004; Selvaraj et al., 2009), the inclusion of comparisons of both current and former users to Controls in the same analysis would potentially confound its interpretation.

Analytic Strategy

A criterion agreement established by the author of this thesis (KD) and his Director of Studies (PM) for the initial categorisation of a task, with other supervisors, asked to challenge any classifications they considered inappropriate. In the interests of consistency within the meta-analyses, all comparisons of Cannabis/alcohol use performance were with the performance of non-drug using controls. In this way, all inter-group comparisons

included in meta-analyses had some degree of matching for the use of other drugs to diminish the potentially confounding effect of their use on the measures of task performance. As indicated previously, the study coded inter-group performance differences as “negative” if they were consistent with Cannabis and Binge users' performance impairment in comparison with the scores of the controls and as positive where users performed at a higher level than the control group.

Meta-analyses using the means, standard deviations, and group sizes (*N*) for all DVs from tasks in the respective categories. Within each analysis, each study was represented by mean effect sizes for all appropriate comparisons, which in turn represented all of the DVs compared. In this way, our meta-analyses avoided the distorting effects of using multiple effect sizes where outcomes are not independent because of the same sub-samples of participants having in various comparisons. The effect size statistic chosen was Hedges *g*, as this controls for distortions arising from small samples in the more commonly used Cohen's *d* statistic (Borenstein et al., 2009). Rosenthal's Fail-safe *N* is reported for each meta-analysis, indicating the minimum number of studies that would be required to render the result non-significant. The researchers included only studies in peer-reviewed journals in this review. This statistic is important in the interpretation of meta-analytic results. Given the possibility that studies reporting significant performance differences between binge drinking/ cannabis smoking users and controls may be more likely to be published than those reporting no difference. The analysis could not make assumptions for fixed-effects models given the variety of visuospatial tasks employed. The examiners mad an a priori decision to only examine results for random-effects models. The choice of random-effects models in this way, rather than upon the consequences for heterogeneity in a fixed-effects model, is currently recommended practice in a meta-analysis (Borenstein et al., 2009). In addition to these performance comparisons between binge drinkers/ cannabis smokers and controls, meta-regression (method of moments) using estimated lifetime alcohol consumption (in units) and cannabis (in cigarettes) as a predictor of effect sizes, where estimates were available in this form. The analysis coded effect sizes consistent with a binge/cannabis-related effect as “negative”, a relationship between these and increasing alcohol and cannabis consumption would yield a negative coefficient. Borenstein et al. Recommend at least ten studies (or independent subgroups within studies) per predictor in a meta-regression for

adequate statistical power. Meta-analyses used COMPREHENSIVE META-ANALYSIS (CMA 2.0™ Biostat, Englewood, New Jersey) software

Results

Table 1 outlines the three levels of the exclusion criteria; the removal of papers at each stage and how the articles met specific corresponding inclusion and exclusion criteria. For Level 1 papers were excluded that while related to the research question where conducted on animals and as such, not suitable for inclusion, for example, Cha (2007). Following this, the next most relevant determinant of exclusion was papers that were not related to the field of study, in that they were from disciplines not related to the task. Such articles belonged to disciplines such as criminology and law and is a notable case that was generated by the scoping search. One study crossed over from the law to dentistry (Underwood et al. 2000). The exclusion criteria removed an additional paper, that of a review article, which while related to the field was a literature review and as such, offered up no new research. (Solowij, 2008).

At level 2, the study removed papers because the analysis regarded participants as polydrug users (other than cannabis or alcohol). There was a degree of flexibility in this stage where individuals reported using drugs other than cannabis and alcohol. However, researchers would include a paper if results indicated that the use of other drug use was low and was not considered a habitual drug-taking behaviour. The second-largest exclusion criteria at this level were that the studies where medical neuroimaging studies and whilst carried out the relevant neurocognitive tests did not report the mean or standard. Instead, they tended to report exclusively on neuroimaging data such as specific brain activation sites in the two groups. Tapert et al. (2004) focused in on binge drinking, and visuospatial working memory is concerned with cortical brain activation and the use of BOLD imaging, with no mean or standard deviations recorded. At this stage, three papers also reported on cognitive findings of individuals who were not abstinent at the time of testing. Specifically, the researchers administered synthetic variants of the drugs taken to participants and reported on neurocognitive functioning whilst under the influence of drugs (Hunault et al. 2009, Dumont et al. 2011 and Weinstein et al. 2008).

The last exclusion criteria at this level identified three longitudinal papers which reported on individual's neurocognitive performance at different times during a treatment intervention, as such, there was no control group to compare to (Payne et al. 2000, Teichner et al. 2001 and Zammit et al. 2002). The Final level of the examination was able to identify three papers that were suitable for exclusion. In all three cases the authors of the articles, whilst reporting on relevant neurocognitive tests failed to report any means and the analysis converted standard deviations into *z* scores and the analysis could extract no relevant data, (Medina et al. 20071, Medina et al. 20072 and Padula et al. 2007).

Table 1: Summary of exclusion criteria and umber of papers removed at each level

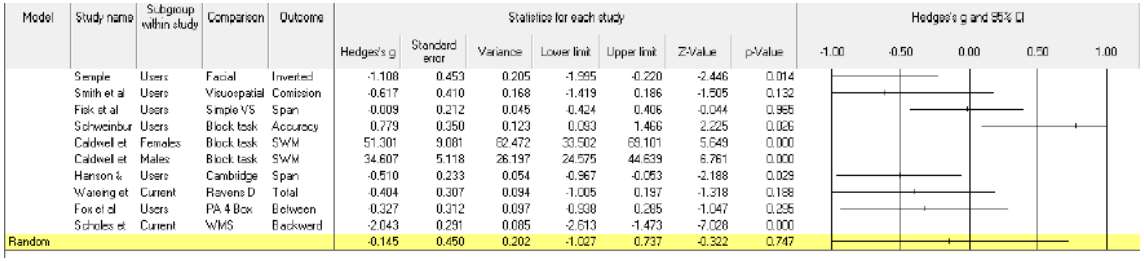
Level 1	**Level 2**	**Level 3**
Not related to the field of study (*N* =101)	Cognitive Scores not reported (*N* = 18)	Failed to Report Means and Standard Deviations (*N* = 61)
Animal Study (*N* = 108)	No Control Group (*N* = 3)	
Review Article (*N* = 1)	All groups were Poly-Drug Users (*N*= 29)	

Table 2: Summary of studies on binge drinking and cannabis smoking using visuospatial tasks included in this study.

		Group1 (polydrug)					Group 2 (controls)					Direction
Study	**Test Measures**	**Mean**	***SD***	***N***	**Cannabis measure (joints)**	**Alcohol measure (units)**	**Mean**	***SD***	***N***	**Cannabis measure (joints)**	**Alcohol measure (units)**	
Semple (2003)	BDII	0.77	0.12	10	27.8	14.4	0.86	0.15	11	1.0	13.5	Positive
		0.53	0.13				0.38	0.13				Negative
Smith et al. (2010)	Spatial Delayed Response Task	0.47	0.04	10	8.82	4.77	0.50	0.03	14	1.12	2.00	Negative
Fisk et al. (2011)	Alphabetic and random	2.05	1.41		3009.15	18.30	2.83	1.34		145.44	9.58	Negative
Schweinburg et al. (2005)	Trail Making Test	91.00	9.0	19	12.80	42.27	86	5.0	15	5.0	0.11	Negative
Caldwell et al. (2005)	Trail Making Test	89.83	0.06	18	53.14	4.80	84.84	0.11	21	1.33	0.00	Equal
		90.75	0.05		38.28	1.38	88.33	0.08		6.25	0.67	Equal
Hanson (2010)	Spatial Delayed Response Task	-0.18	1.08	29	2396	5.3	0.32	0.75	52	2.1	1.2	Negative
Wareing et al. (2004)	Alphabetic and random letter generation task	2.5	7.1	18	7	6	2.30	0.88	10	5	16	Negative

Fox (2002)	CANTAB (ID/ED)	32.7	5.3	10	275	8.7	32.0	4.1	10	450	10.7	Negative
Scholes et al (2010)	Wechsler Memory Scale (WMS)	8.88 9.17	0.60 0.58	36	10	2	10.23 11.26	0.50 0.44	22	1.0	3.5	Negative

Figure 2: Meta-analytic results and forest plot



Model	Study name	Subgroup within study	Comparison	Outcome	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Semple	Users	Facial	Inverted	-1.108	0.453	0.205	-1.995	-0.220	-2.446	0.014
	Smith et al	Users	Visuospatial	Comission	-0.617	0.410	0.168	-1.419	0.186	-1.505	0.132
	Fisk et al	Users	Simple VS	Span	-0.009	0.212	0.045	-0.424	0.406	-0.044	0.965
	Schweinbur	Users	Block task	Accuracy	0.779	0.350	0.123	0.093	1.466	2.225	0.026
	Caldwell et	Females	Block task	SWM	51.301	9.081	82.472	33.502	69.101	5.649	0.000
	Caldwell et	Males	Block task	SWM	34.607	5.118	26.197	24.575	44.639	6.761	0.000
	Hanson &	Users	Cambridge	Span	-0.510	0.233	0.054	-0.967	-0.053	-2.188	0.029
	Waring et	Current	Ravens D	Total	-0.404	0.307	0.094	-1.005	0.197	-1.318	0.188
	Fox et al	Users	PA 4 Box	Between	-0.327	0.312	0.097	-0.938	0.285	-1.047	0.295
	Scholes et	Current	WMS	Backward	-2.043	0.291	0.085	-2.613	-1.473	-7.028	0.000
Random					-0.145	0.450	0.202	-1.027	0.737	-0.322	0.747

Means and Standard deviations for alcohol and cannabis consumption across the nine papers included in this study found in Table 2, as can details of the VSWM task employed and the direction of the study's findings. The statistical findings for the systematic review utilising a random-effects model in Figure 2. To summarise the main statistical findings, the 9 comparisons included in the meta-analysis yielded a non-significant mean weighted effect size, failing to show poorer task performance by the cannabis Polydrug users (Hedges g = -0.154; 95% confidence interval (*CI*) -1.027 (*Lower*) to -0.737 (*Upper*); z = - 0.322, p = .0747, two-tailed). However, given the closeness of the p-value to significance, Rosenthal's Fail-Safe N was calculated and indicated that the study would require 60 studies to render the observed p non-significant.

Discussion

The results from the Meta-Analysis reported that there was no significant observable effect for Visuospatial working memory and polydrug use. Given the prevalence of Binge Drinking and Cannabis Smoking within the general population of not just the UK but multiple countries worldwide (Anderson et al. 2006) the findings suggest that this paper may be relevant to the policies and practices of governments and health agencies both nationally and internationally.

The finding that binge drinking cannabis smokers did not appear to show impaired visuospatial memory performance when compared to controls is reflective of the indeterminate nature of results from within the academic literature, with papers reporting both significant and non-significant results (Gamito et al.,2014 and Hadjiefthyvoulou et al.,2012). Indeed, it is a salient argument to make that these results could be reflective of the diffuse nature of VSWM networking within the prefrontal cortex (Zimmer, 2008). Indeed, compromised functioning in one or more of the network of brain areas recruited in the processing of Visuospatial information could still be taking place, but not being detected by the results from this analysis. Tres (2014) reported that traditional VSWM tests tend to focus upon aspects of VSWM networked through the PFC, which in itself is limiting as VSWM networks through the parietal, temporal and occipital lobes. This widespread dispersal of brain areas, therefore, makes it challenging to interoperate the results of this study.

In conclusion, the study failed to demonstrate those binge drinkers who smoked cannabis performed worse on visuospatial tasks when compared to non-cannabis smoking, non-binge drinking controls. The paper does acknowledge that there are limitations to the study, such as limiting the paper inclusion to English Language only. Though the fail-safe *N* statistic suggests that the limitations identified, do not preclude the review from offering insight into drug use and visuospatial impairment. It is therefore worth noting that research in this field is vital for public health as visual and spatial working memory are essential for successful navigation through many daily activities such as driving, operating machinery and for social wellbeings such as in sports and recreation. Whilst neural structures return to a baseline position after three months abstinence. However, this does not necessarily equate to a return to baseline for neurocognitive functions. It is challenging to assess neurocognitive functioning in the natural environment however as everyday visual and spatial tasks also require the recruitment of different working memory and executive functions for successful completion, which in turn recruits other neurological structures to facilitate this activity. Despite the limitations, the use of laboratory-based experimentation represents a "gold standard" Visuospatial assessment. Future investigations into visuospatial working memory would benefit from employing an empirical approach.

Chapter 4:
Verbal Memory Performance in Binge Drinkers Who Smoke Cannabis, Literature review and Meta-Analysis

Introduction

Chapter 2 discusses the effects of binge drinking and cannabis smoking combinations on executive functioning task performance more broadly. However, a scoping search of the academic literature (as described in the Methods section of this chapter) notes that verbal working memory is as widely researched an EF domain as VSWM, with regards to binge drinking and cannabis smoking.

Marvel and Desmond (2016) the authors regard the verbal component of working memory as a cognitive process facilitating the storage of speech-related information. Baddeley (1992) provides a framework with the conceptualisation on the process. Maintenance of verbal communication occurs via a cognitive process known as the phonological loop. The loop contains two components: (1) a passive storage process, relatively quick speech-based information that lasts 1–2 s, and (2) an active articulatory control process. Baddley described the process by which verbal communication proceeds via this two-stage mechanism. At stage one, stimuli with a visual aspect such as printed words translated into a "phonological representation.". Aurally presented information requires no such translation. The maintenance of information occurs via subvocal repetition, a process referred to as the phonological loop.

As with the research from chapter 3, the academic literature has also found that consumption of binging levels of alcohol results in verbal working memory deficits. For example. In a meta-analysis conducted by Lannoy et al. (2019), the author reported that binge drinking is associated with impairments to verbal working memory. Specifically, the author noted that those individuals who meet the DSM-V criteria for binge drinking recorded significantly lower test scores on multiple verbal working memory paradigms, including the California Oral Word Test (COWAT). In conjunction with these findings, the Lannoy argued that previous meta-analyses into this issue have been insufficient due to search hits. The traditional belief was that there was no association between verbal

working memory and binge drinking. However, Lannoy questioned this, based on the assumption of flawed scoping searches. With this addressed, Lannoy argues that a more detailed analysis of the literature provides evidence of significant verbal working memory impairments in binge drinkers compared to controls.

Research has also reported deficits to verbal working memory task impairment in cannabis smoking populations. For example, Radomann et al. (2019) reported a causal relationship between cannabis consumption and verbal working memory. Specifically, the author noted that in the analysis of "verbal" task score of 141 current cannabis smokers, reported lower verbal task performance scores on the California Verbal Learning Test (CVLT II) task scores.

However, there is no consensus on this issue within the academic literature, with a significant body of research also indicating that there is no significant effect for verbal working memory from either binge drinking or cannabis smoking populations. For example in a meta-analysis conducted by Cabria et al. (2018), the author reported that the current consensus with regards to binge drinking induced working memory defects is that this form of substance misuse has no negative impact upon verbal working memory task performance. Meta-analytic results reported by Crean et al., (2011) said that the studies conducted into Cannabis and verbal working memory are limited, however, and the reviews only serve to emphasise the indeterminate nature of the research in the field today. The author notes that out of the four studies that investigated this aspect of working memory, three found no significant difference between cannabis users and controls.

However advances in the field of imaging technology has afforded researchers access to a broader array of techniques that could potentially account for the indeterminate nature of results found thus far (Casey et al., 2005). Introduction of these approaches to the field of substance misuse has been able to provide researchers with evidence of physiological damage caused by both THC and ethanol, even when no apparent behavioural impairment is evident (Dickerson et al., 2007). For example, Cservenka et al. (2012) conducted a study on binge drinking and verbal working memory via a variant of the word fluency test. Results indicated that while the binge drinkers reported a slower response times. The

study could observe no other significant difference. However, through the use of MRI, results indicated that the binge drinkers reported a statistically significant reduction in prefrontal cortex activity during the task. The authors concluded that not only was verbal working memory networked through the PFC. But continued binge drinking could potentially result in a progressive degradation of Verbal Working Memory task performance, as activations levels continually decrease to a point where task demands fail.

Neuroimaging technology has also implicated cannabis consumption to prefrontal cortex damage during verbal working memory task performance. For example, Jagger et al. (2006) conducted a study in which the study compared ten active cannabis smokers to ten non-smoking controls on a battery of verbal working memory tasks. Results indicated that the cannabis users displayed comparable task performance scores to the control group during the Working Memory task and the selective attention task. At the same time, preliminary neuroimaging results indicated that cannabis users did not differ from controls in terms of overall patterns of brain activity in the regions involved in these cognitive functions. A more detailed analysis of prefrontal cortex structures indicted that cannabis users displayed a significant alteration in brain activity in the left superior parietal cortex.

The evidence presented thus far suggests that both cannabis and alcohol cause impairments to verbal working memory task performance. The neurocognitive data presented in this chapter raises the issue of alcohol metabolites and neurotoxicity. Toosi et al. (2019) and Chowdury et al. (2019)

This present study uses systematic review and meta-analytic methodology in a preliminary investigation of the respective relationships between combined Cannabis and alcohol consumption, and verbal working memory task performance.

Method

Searching Strategy

The study searched all abstracting databases comprising the United Kingdom National Health Service, Evidence Health Information Resource, Academic based research databases, specifically: PsycInfo, Pubmed, Cinall and Web of Science database using the following key terms: Cannabis, Verbal, Verbal-Memory and Verbal-Memory performance. These terms were also 'exploded' using the relevant database thesaurus to ensure completeness of data. The analysis restricted the search to English language publications with human participants. Other inclusion criteria were that studies had to be in peer-reviewed journals and to be reporting new findings (including attempted replications) regarding verbal memory performance in the context of cannabis use. Participants needed to have been abstinent from Cannabis and other drugs of misuse at the time of testing for approximately one month, to remove the potential methodological confound of THC intoxication. The study excluded participants under the influence of or another drug, animal studies and studies published in a language other than English. The review also excluded if they were in the form of dissertations, conference presentations, reviews or meta-analyses. The analysis included all relevant studies published before June 2014 (the time of the search). Inclusion in the review sample did not automatically imply inclusion in the meta-analysis, as the need to produce a meaningful summary effect size required some degree of design similarity between the primary studies. Inclusion in the meta-analysis needed the analysis to compare the performance of cannabis users to that of control participants. Inclusion in the review sample did not automatically imply inclusion in meta-analyses, as additional criteria regarding study design, tasks employed, and the reporting of data were relevant to these decisions are in the Analytic Strategy section.

Data extraction

For each study included in the review, the study recorded the analysis details for each subgroup of Participants regarding, number of participants, alcohol and cannabis consumption, types of verbal-memory task employed and corresponding means and standard deviations, table 4 reports upon the data. The study solely based allocation to either the control or experimental upon the level of alcohol drinking in units and cannabis cigarettes smoked where research papers intended to compare binge drinkers/ cannabis

smokers with a control group of non-bingers/ cannabis smokers, as consistent with the study based group allocation on the allocation within the original documents. Where intention was not clear, for instance (Hadjiefthyvoulou 2011) mean scores for alcohol use that did not meet the criteria for Binge Drinking and no record of cannabis smoking resulted in automatic inclusion into the "control" group. The converse automatically resulted in inclusion into the "Experimental Group". Where papers failed to report the average number of alcohol units drunk, and amount cannabis smoked over the three months, (Dougherty 2013). The study then used the calculated means for group allocation in terms of polydrug use. The research permitted minor infringements to the inclusion criteria. Cunah (2010) allowed low levels of cannabis exposure (having tried it once in their lifetime, but still within the one-month washout timeframe) to into the control group. There appears to be a trend of laxity towards drug-taking behaviour by the authors. The study extended this pattern to participants who had experimented with other drugs, where the use of illicit substance did not represent a pattern of behaviour. The study developed this approach to persistent legal drug-taking in instances of long term exposure to legally available substances of abuse such as tobacco.

Although all participants had been abstinent from Cannabis and other illegal drugs at the time of testing, the results did not make performance comparisons with groups designated as former users. Given the evidence that compromised brain functioning may return to levels consistent with that of controls in former users (Buchert et al.,2004; Selvaraj et al., 2009). The inclusion of comparisons of both current and former users to Controls in the same analysis would potentially confound its interpretation such as in the paper by Pope (2001) where the study reported the data from existing users and controls.

Meta-analytic strategy

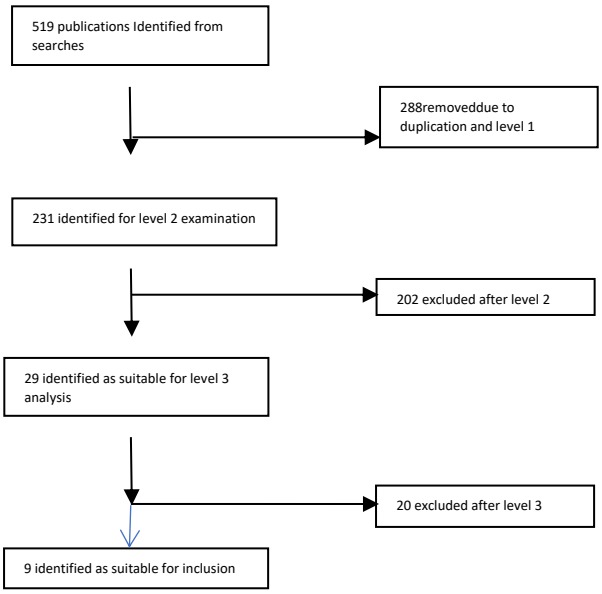
The analysis adopted a consistent strategy within the meta-analysis, whereby the study compared all cannabis/ binge drinkers task performance to that of non-binge drinking/ non-cannabis smoking controls. This approach ensures more power for the matching of the intergroup comparisons. As well as the use of additional legal and illicit drugs (so that we did not include chaotic polydrug users, who regularly take other substances), and thus diminished potential methodological confounds arising from their use.

The meta-analysis used the means, standard deviations, and group sizes (n) for all DVs from the verbal-memory tasks. Outcomes coded the information so that worse task performance by cannabis users appeared as an adverse effect size whilst in instances where the experimental group performed better than the control group the study encoded a positive effect size into the meta-analysis. This approach benefited the meta-analysis as it can avoid the distortion inherent in analysing multiple effect sizes where outcomes are not independent because of the same sub-samples of participants in various comparisons. Given the variety of verbal-memory tasks employed, and the heterogeneous nature of the participant samples and their drug use, results could not make the assumptions for fixed-effects models. The researchers decided upon an "*a priori"* decision only to examine outcomes for random-effects models. The researchers chose Hedges *g* effect size statistic, to be able to control for any distortions that may arise within the data, a phenomenon common in papers such as this. That use small samples, as opposed to the more commonly used Cohen's *d* statistic (Borenstein et al., 2009). The meta-analysis also utilised Rosenthal's Fail-safe *N* statistic, which indicates the minimum number of studies that would be required to render the result of this analysis non-significant. This statistic is vital in this review as it focused solely upon studies from peer-reviewed journals, given the propensity for journals to publish studies that report significant performance differences between binge drinking/ cannabis smoking users and controls. In this instance, the choice of random effects model is currently recommended practice in a meta-analysis (Borenstein et al., 2009). The meta-analysis used COMPREHENSIVE META-ANALYSIS (CMA 2.0™ Biostat, Englewood, New Jersey) software.

Results

Figure 3, outlines the search process and corresponding inclusion and exclusion levels, for this study, the term 'publication' is used to emphasise the diversity of items initially identified. Level 1 examination against the inclusion/exclusion criteria excluded papers where, for example, the search terms' binge drinking' or "Cannabis', resulted in the identification of publications from the realms of Criminology or Law. The study removed duplications in papers. The study identified two levels of examination against the inclusion/exclusion criteria for the remaining 231 articles. These two levels differentiated by the extent of the analysis required. For example, in some cases, it was possible to identify animal studies and reviews from their abstracts and a preliminary examination of the main text. These findings would constitute a Level 2 examination against the inclusion/exclusion criteria. The study examined the 29 studies identified as receiving a Level 3 examination against the inclusion/exclusion criteria in detail to assess their compatibility with these criteria. Details of the nine studies included in the review are in Table 2. In table 1 can be found a detailed summary of the three levels of examination and subsequent exclusion criteria.

Figure 3: Mapping of the literature search process.



1Examination by title and source

2Examination by an abstract and preliminary reading of the text

3Examination by a detailed reading of the text

Figure 3 describes the search process for the systematic review. Papers were either retained or deleted from the study based upon a 3-level suitability analysis. At level 1 papers removed were from outside the discipline, Markowitz (2005), was concerned with the relationship between the taxation of alcohol, availability of illegal drugs such as Cannabis and the level of criminal behaviour. The second-largest trigger for exclusion at this level were papers translated into English; indeed, upon appraisal of this, it appears that the majority were from Scandinavian such as Ringen et al. (2013). The third most common exclusion criteria were that of animal studies. The study of rats limits their relevance to human behaviour and deemed inappropriate for inclusion, such as the paper by Fehr (1976) into learning impairment in rats exposed to alcohol and THC. Three Meta-analyses were also uncovered at this stage and subsequently removed (Verbaten 2003, Yücel et al. 2012, Potvin et al. 2008) and finally, the appearance of a non-peer-reviewed paper (Argenter, 1996). Studies removed at At level 2, we're concerned with reporting on neuroimaging data. They did concern themselves with verbal memory performance and failed to record any mean scores. Desmond et al. (2003) noted exclusion for papers looking at polydrug use, e.g. Rosselli (1996). The study also excluded if participants were not abstinent at the time of testing (Parker 1980). The study also excluded papers if they were longitudinal and in some instances, a control group was absent entirely. Schott et al. (2003) describe the individual case study of a 68-year-old man. At level 3, fewer papers were removed level (N=20) owing to inappropriate reporting strategies, or based on a failure to convey pertinent information. Squeglia et al. (2009) transformed the means and standard deviations into z scores which would distort the overall result if included. As these represent a different metric and as such are no longer measures of performance. Whilst Schweinsburg et al. (2010) failed to report any means and standard deviation; consequently, the study could not extract the relevant data. Table 3 summarises the exclusion of papers at each level of the search.

Table 3: Mapping of the literature search process

Level 1	**Level 2**	**Level 3**
Paper did not relate to the field of study (*N*=207)	No means and standard deviations Reported Neuroimaging data only (*N*= 105)	Transformation of means into z scores (*N*=2)
Animal study (*N*=28)	Control and Experimental group were polydrug users (*N*=52)	No means or Standard Deviations reported (*N*=18)
Paper not translated from a foreign language to English (*N*=49)	groups weres intoxicated at the time of testing (*N*=36)	
Not Peer Reviewed (*N*=1)	The Experiment had no control group (*N*=9)	
Meta-analysis/ review article. (*N*=3)		

Table 4 summarises the alcohol and cannabis consumption mean scores as well as the mean scores for the VWM task performance measures. Figure 4 reports upon the main statistical findings; results indicated that there was a large and statistically significant mean weighted effect size. Results showed lower task performance by the poly-drug users (Hedges g = -0.535; 95% confidence interval (*CI*) -0.806 (*Lower*) to -0.264 (*Upper*); z = - 3.871, $p < 0.000$, two-tailed). Calculation of Rosenthal's Fail-Safe *N* indicated that studies would require 135 papers to render the observed *P* non-significant.

Table 4: Summary of studies on binge drinking and cannabis smoking using verbal working memory tasks included in this study.

Study		Group1 (polydrug)					Group 2 (controls)					Direction
	Test Measures	**Mean**	***SD***	***N***	**Cannabis measure (joints)**	**Alcohol measure (units)**	**Mean**	***SD***	***N***	**Cannabis measure (joints)**	**Alcohol measure (units)**	
Cunah et al. 2010	**Frontal Assessment Battery**			30	5.69	4.61			32	0.4	0.28	
	Conceptualisation	2.25	.08				.65	.11				Negative
	Mental Flexibility	2.39	.13				2.87	.06				Negative
	Motor Programming	2.07	.14				2.71	.09				Negative
	Sensitivity to Interference	2.75	.08									
	Inhibitory Control	2.61	.11				2.84	.06				Negative
	Environmental Autonomy	3.00	.00				2.58	.15				Negative
Croft 2001	**Verbal Fluency**			18	7762.4	5309.8			31	0.5	3875.3	
	Word	48.0	1.1				48.9	11.6				Negative

	Fluency	24.4	6.0				26.6	4.2				Negative
	Coughlan list and design learning											
	List 1-6	56.3	9.0				62.4	7.7				Negative
	List 6	11.8	3.0				13.2	1.6				Negative
	List B	6.5	2.2				8.5	2.7				Negative
	Design 1-5	34.9	8.6				39.9	6.5				Negative
	Design 6	7.3	2.1				8.2	1.7				Negative
	Design B	7.3	2.1				6.7	2.0				Negative
Dougher ty 2012	**Buschke Selective Reminding Test**	112.5	18.2	45	36.0	7.0	121.2	15.1	48	0.0	2.0	Negative
	Total Recall						90.7	36.1				
Gonzale z et al. (2012)	**Hopkins Verbal Learning Score**			65	60	108			65	0	24	
	Immediate Recall	79	36.8									Negative
	Delayed	-.82	1.33				-.26	1.16				Negative
	Recognition	-.89	1.30				-.41	1.13				Negative
	Discriminability	-.13	1.08				-.10	2.63				Negative

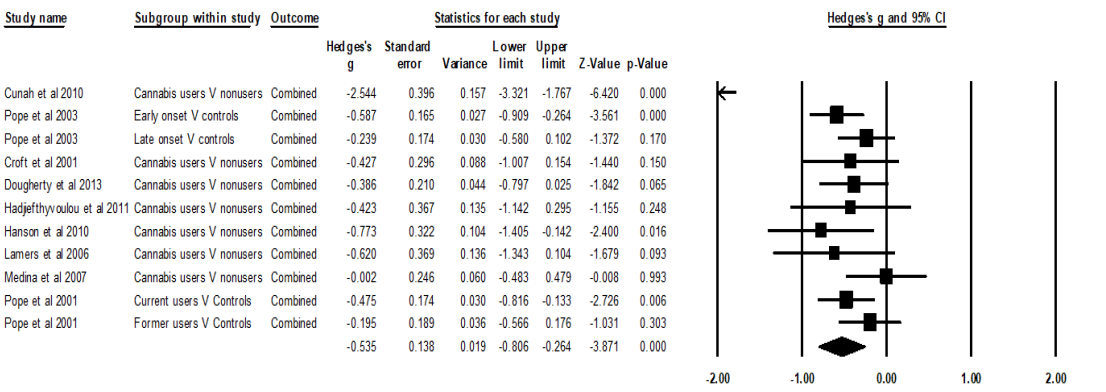
Hadjieft	**RAVALT**			18	0.50	15.8			12	0	9.47	
hyvoulo	Learning T-T5	40.58	11.1				45.22	9.60				Negative
u et al	Proactive	1.58	1				0.94	1.47				Negative
(2011)	Retroactive	2.0	1.38				1.39	1.46				Negative
	Decay	2.0	1.86				1.22	1.26				Negative
Medina	**WMS Logical Memory**			31	170.72	44.06			34	0.0	6.44	
(2007)												
	1st recall	25.3	6.1				26.3	6.3				Negative
	Logical memory recognition	26.1	3.0				26.5	2.7				Negative
	Verbal List learning	51.7	8.5				53.8	9.4				Negative
	CVLT 2 Total recall	0.7	0.8				0.6	1.2				Negative
Lamers	**RAVALT** Recall											
2006												
	RAVALT Delayed Recall	52.3	7.6	15	1581.6	779.6	60.0	5.3	15	1.2	317.5	Negative
		10.7	3.5	63	18720	4700	13.1	1.5	72	10	2800	Negative

				45	11000	3900			
Pope	**Buschke Selective**								
2001	**Reminding Test**								
	Current Users								
	Total Recall								
	Day 0	104.5	15.0				113.6	16.3	Negative
	Day 1	106.7	17.0				115.5	15.7	Negative
	Day 7	111.7	15.4				120.9	13.6	Negative
	Day 28	116.4	12.9				121.1	13.6	Negative
	Long-Term Storage								
	Day 0	96.5	9.1				108.6	21.9	Negative
	Day 1	99.4	22.7				109.0	21.2	Negative
	Day 7	105.7	22.5				117.2	16.6	Negative
	Day 28	112.4	22.0				117.2	19.0	Negative
	Consistent Long Term								
	Retrieval								
	Day 0	58.0	29.2				77.1	33.0	Negative
	Day 1	62.0	33.4				81.7	36.3	Negative
	Day 7	70.8	32.8				91.5	35.2	Negative
	Day 28	79.4	31.2				91.9	31.7	Negative
	30 Minutes Delayed								
	Free Recall								
	Day 0	8.8	2.3				9.7	2.4	Negative

Day 1	8.3	2.7	9.6	2.6	Negative
Day 7	8.3	2.6	10.1	2.0	Negative
Day 28	8.6	2.3	10.2	2.2	Negative
Former Users					
Total Recall					
Day 0	109.1	13.4	113.6	16.3	Negative
Day 1	114.9	11.3	115.5	15.7	Negative
Day 7	118.7	12.9	120.9	13.6	Negative
Day 28	117.9	13.5	121.1	13.6	Negative
Long-Term Storage					
Day 0	104.5	21.1	108.6	21.9	
Day 1	108.2	16.5	109.0	21.2	Negative
Day 7	115.1	18.3	117.2	16.6	Negative
Day 28	112.4	19.6	117.2	19.0	Negative
					Negative
Consistent Long Term					
Retrieval	64.4	27.7	77.1	33.0	Negative
Day 0	75.0	28.4	81.7	36.3	Negative
Day 1	86.9	30.9	91.5	35.2	Negative
Day 7	82.2	32.6	91.9	31.7	Negative

	Day 28											
	30 Minutes Delayed											
	Free Recall											
	Day 0	9.4	2.2				9.7	2.4				Negative
	Day 1	9.6	2.4				9.6	2.6				Negative
	Day 7	9.9	2.3				10.1	2.0				Negative
	Day 28	9.2	2.5				10.2	2.2				Negative
				21	465.0	54.4			19	1.2	3.2	
Hanson	**HVLT R**											
(2010)	Trial 1 recall	6.1	1.4				7.4	1.8				Negative
	Trial 2 recall	8.3	1.2				9.5	1.8				Negative

Figure 4: Meta-Analytic results and forest plots



Study name	Subgroup within study	Outcome	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Cunah et al 2010	Cannabis users V nonusers	Combined	-2.544	0.396	0.157	-3.321	-1.767	-6.420	0.000
Pope et al 2003	Early onset V controls	Combined	-0.587	0.165	0.027	-0.909	-0.264	-3.561	0.000
Pope et al 2003	Late onset V controls	Combined	-0.239	0.174	0.030	-0.580	0.102	-1.372	0.170
Croft et al 2001	Cannabis users V nonusers	Combined	-0.427	0.296	0.088	-1.007	0.154	-1.440	0.150
Dougherty et al 2013	Cannabis users V nonusers	Combined	-0.386	0.210	0.044	-0.797	0.025	-1.842	0.065
Hadjefthyvoulou et al 2011	Cannabis users V nonusers	Combined	-0.423	0.367	0.135	-1.142	0.295	-1.155	0.248
Hanson et al 2010	Cannabis users V nonusers	Combined	-0.773	0.322	0.104	-1.405	-0.142	-2.400	0.016
Lamers et al 2006	Cannabis users V nonusers	Combined	-0.620	0.369	0.136	-1.343	0.104	-1.679	0.093
Medina et al 2007	Cannabis users V nonusers	Combined	-0.002	0.246	0.060	-0.483	0.479	-0.008	0.993
Pope et al 2001	Current users V Controls	Combined	-0.475	0.174	0.030	-0.816	-0.133	-2.726	0.006
Pope et al 2001	Former users V Controls	Combined	-0.195	0.189	0.036	-0.566	0.176	-1.031	0.303
			-0.535	0.138	0.019	-0.806	-0.264	-3.871	0.000

Discussion

As with Visuospatial working memory, the results from this meta-analysis demonstrated a reduction in verbal memory performance by the experimental group, when compared to non-binge drinking/ cannabis smoking controls. Again, as with the previous study into visuospatial working memory, this suggests that given the prevalence of binge drinking and cannabis smoking within the general population of most major western countries (Anderson et al. 2006) that these results would have profound implications for governments and health agencies both nationally and internationally. Indeed, these findings are consistent with observations made in the academic literature which have noted that alcohol and Cannabis can induce neurological damage to cortical structures associated with the processing of verbal memory specifically: the prefrontal, parietal, temporal and occipital lobes (Roberts & Montgomery, 2015; Montgomery & Fisk, 2012). Thus, it is reasonable to assume that that the act of polydrug use in this fashion may result in compromised functioning in one or more of these network of brain areas (Kelley et al. 1997). However, the widespread dispersal of these structures represents a significant obstacle in the association of deficits in task performance to a specific cortical system.

Upon initial consideration of the data gathered the findings in the review suggests lower verbal working memory task performance in polydrug users. However, the neurological capability would also depend upon various specific potential confounds that can distort the relationship

such as the age of onset of drug-taking behaviour, premorbid IQ, Polydrug history, as well as genetic variables. Zakhari and Li (2007) were able to demonstrate a relationship between the variability of BAC in heavy alcohol drinkers and genetic variants. Cytochrome P450 2E1 (CYP2E1) isoform affects the absorption rate of ethanol; this has been implicated in predisposing individuals to alcohol dependence and susceptibility to alcohol-induced liver damage and neurocognitive impairment. Watanabe et al. (2007) suggested that Cytochrome P450 enzymes metabolise THC and cannabinol. Therefore genetic variation would undoubtedly affect absorption rates of THC and affect cannabis-induced neurocognition. Thus, future research would benefit from considering genetic variation in the population sample.

In conclusion, the study demonstrated a relationship between cannabis smoking, binge drinking and decreased verbal memory performance, when compared to a control group on non-binging/ cannabis smoking controls. However, the paper does suffer from some specific limitations that future researchers need to address regarding this relationship—potential confounding influence of additional substances in the population sample. Additionally, the paper by Cunah et al., (2010) appears to have a comparatively strong Hedges *g*, and as such, it may be exerting an undue influence on the meta-analytic results. The review also limited itself to the inclusion of English Language only papers the report also failed to account for information within "grey literature" such as unpublished conference papers, internal research reports within institutions (NHS). Despite the limitations that were identified the results from the study demonstrate a Mean weighted effect size that was both large and statistically significant with a robust Fail-Safe *N* statistic. Therefore, though the paper has its limitations, they do not preclude the study from offering up insight into polydrug use and verbal memory impairment. Indeed, research in this area must continue since issues surrounding drug use are a critical public health concern. Since verbal working memory is an essential cognitive tool for successful navigation through many daily activities such as following instructions and for social wellbeing, any issues that affect the functionality of this are of importance for public health. Whilst neural structures have returned to a baseline position after three months abstinence (Montgomery et al., 2012) this does not necessarily equate to a return to baseline for neurocognitive functions. However, it is challenging to assess neurocognitive functioning in the natural environment. Everyday Verbal working memory tasks also require the recruitment of different working memory and executive functions for successful completion, which in turn recruits other neurological structures to facilitate this activity. Despite the limitations, the use of laboratory-based experimentation

represents a "gold standard" verbal memory assessment, and as such future investigation must continue with this approach.

Chapter 5

Demographic and Background details of the sample for this thesis

Introduction

Research from within the substance misuse literature has developed theoretical frameworks that have served to highlight demographic indices. These psychological and behavioural traits serve as risk factors for both heavy social drinking (HSD) and cannabis consumption (Gonzales et al., 2017). In developing a deeper understanding of the consequences of HSD cannabis smoking polydrug use, it is essential first to consider how polydrug users compare to single drug users and controls with regards to these identified indices. Within the scientific literature that there are significant age and gender biases within both HSD and cannabis smoking populations. In a study conducted by Tu and Ratner (2009) on relative age and gender differences concerning substance misuse, of those individuals who reported drinking alcohol, a disproportionate number of males reported excessive levels of consumption. Results indicated that 63% of males and 42% of females drank more than sensible weekly limits (above six units for females and 7 for males) with 56% of males classified as 'binge drinking'. Analysis of illicit drug misuse in this population indicated that 55% of the male students also reported cannabis use at least once since starting university.

Further investigation revealed that 8% of males reported current regular use at least once a week. These findings are similar to those of Webb (2007) who in an earlier cross-sectional nationwide study said that of those questioned, 23% of young males reportedly drank to levels regarded as Binge drinking compared with 10% for females. Prevalence of cannabis use was highest in males, of whom 27% reported regular weekly use compared with 9% for females. Also, males said experience with other illicit drugs, with 64–71% reporting experience ecstasy at least once.

Analysis of substance misuse indices for both alcohol and cannabis misuse in the UK and USA indicate that young adult males (between the ages of 18 to 21) tend to report statistically significant higher rates of both cannabis consumption and instances of heavy episodic drinking. Both cannabis consumption and heavy social drinking are severe threats to the intellectual, psychological and physical development of young adults (Boden et al., 2011). For example,

problems of psychosocial adjustment (Falk et al., 2006), reduced hippocampal volumes (De Bellis et al., 2013) and disruptions to the development of neural circuitry (Nguyen-Louie et al., 2018; Weissman et al., 2015). These are associated with the onset of early alcohol consumption, whilst enhanced impairments in cognitive functioning correlate with earlier onset of cannabis consumption (Broyd et al., 2016; Schweinsburg et al., 2008).

It is logical, therefore, to consider the demographic statistics of HSD Cannabis smoking polydrug users to fully appreciate the impact of this form of substance misuse (Wechsler et al., 1994, 2000). In addition to demographic issues such as age and gender, studies examining both HSD and cannabis consumption have identified psychological and behavioural differences when compared to drug naïve controls. Specifically, research has indicated that statistically significant differences exist concerning relative levels of anxiety, depression and impulsiveness (Askénazy et al., 2003). Evidence from within the substance misuse literature has suggested that feelings of anxiety are causally related to both cannabis and alcohol misuse (Breese et al., 2011; Haass-Koffler et al., 2014; Spanagel et al., 2014), as well as to the development and maintenance of substance use disorders (SUD). Etiological explanations have stated that both substances reduce tension/dampen stress responses (Donovan & Marlatt, 1980; Sher & Levenson, 1982). Both used for self-medication (Brady & Lydiard, 1993; Khantzian, 1985; Mueser et al., 1998). Both alcohol and cannabis reduce the unpleasant physiological and cognitive symptoms of stress and anxiety, thereby negatively reinforcing, or increasing, substance misuse behaviour.

One of the most widely used measures for the examination of anxiety levels in both HSD and cannabis smoking populations is that of the Hospital Anxiety and Depression Scale (HADS). Crippa et al. (2009) reported that frequent cannabis users consistently displayed higher prevalence levels of anxiety and anxiety disorders when analysed via the HADS. However, it is unclear if cannabis use increases the risk of developing long-lasting anxiety disorders. Similarly, McCaul et al. (2017) have also noted that individuals identified as HSD reported statistically higher scores for anxiety on the Hospital Anxiety Scale (HADS) when compared to controls. Many hypotheses have attempted to explain these relationships, including neurobiological, environmental and social influences. However, numerous preclinical and human studies examining effects of stress or anxiety on alcohol use and alcohol-related

problems (McCreary & Sadava, 2000; O'Grady et al., 2011; Sayette, 1999; Wand et al., 1998; Young et al., 1990) have been equivocal, showing positive, negative, or no relationship.

Balodis et al. (2009) reported that a comparative difference in levels of impulsiveness also exists in both HSD and cannabis smoking misuse populations. Indeed, findings from within the literature highlight the variability of results from both the HSD and cannabis smoking studies. Trull et al. (2016) reported that cannabis misuse increased levels of trait impulsivity using a real-time self-report measure. Zuckermann and Kuhlmann (2000) report higher impulsivity related to HSD when analysed using the Zuckermann-Kuhlmann personality questionnaire (ZKPQ). However, Lejuez et al. (2009) failed to find a statistically significant effect with regards to substance misuse related differences in impulsivity with regards to either alcohol or cannabis misuse.

In an attempt to explain the contradictory findings regarding impulsivity, Gonzalez et al., (2012) have suggested that individual differences with regards to neurological impairment may play a key role. The author noted that neurocognitive deficits could affect impulsivity levels. Indeed, Cho et al. (2010) have suggested that both alcohol and cannabis impair functioning within the right DLPFC, a region of the brain implicated in the processing of impulsive decision making. Individual differences with regards to the severity of impairment in this region could arguably contribute to the comparative differences in impulsiveness levels currently being observed. Stanford (2009) argues that impulsivity measures are insensitive to subtle alterations in younger HSD's and cannabis smokers. The Barratt impulsivity measure is more reliable in both HSD and cannabis smoking populations. It is, therefore, logical to conclude that an analysis of the comparative differences in levels of, anxiety, depression and impulsivity in polydrug users would be of benefit to understanding the demographic similarities and differences between the two substance misuse groups.

Whilst differences in the psychological characteristics are an essential subject of study in their own right, it is also vital to examine the potential influence of such differences on cognitive task performance. Consequently, the results presented in this chapter, with regards to demographics, psychological variables and substance misuse indices are relevant to all the

chapters within this thesis which present new empirical findings. Future chapters will refer back to this chapter concerning the reporting of these variables.

Method

Design

A 3-participant group design with a control group consisting of non-binging alcohol users (CO) and two experimental groups of binge drinkers (HSD) and binge drinking-cannabis smoking polydrug users (HSDCC) for gathering the data reported in this and subsequent chapters of this thesis. Drug behaviour type served as the independent variable at three levels (i.e. binge drinker, binge drinking cannabis using polydrug user and light social drinking-illicit drug-naive controls). The results of the demographic, psychological and substance misuse indices served as the dependent variables for this chapter. Cognitive test scores and task-related changes in regional cerebral blood flow (rCBF) served as the dependent variables for subsequent chapters.

Participants

Recruitment resulted in Seventy participants from the campus of Edge Hill University. Participants were chosen by opportunity sampling through advertisements placed around the University campus, on the Department of Psychology electronic participation recruitment system (SONA), and by word of mouth. For inclusion, participants had to demonstrate engagement in relevant alcohol and cannabis consumption behaviours for more than three months without any detoxification intervention or long period of abstinence within this time. Controls were those participants who did not meet the American Psychiatric Association's (2013) Diagnostic Statistical Manual-V (DSM-V) criteria for alcohol/substance abuse or dependence. No lifetime exposure to cannabis use or any other illicit drug. Binge drinkers were those participants who met the DSM-V criteria for alcohol abuse, report drinking ≥ 5 and ≥ 4 (for Males and females respectively) units of alcohol in a single drinking session and who have engaged in this behaviour ≥ten days/ month in the past three months (Raffo et al., 2019). Whilst the binge drinking-cannabis smoking polydrug users also met these criteria as well as the DSM-V criteria for substance abuse and ≥ 100-lifetime experiences with marijuana and had used ≥ten days/ months in the last three months.

Exclusion criteria were a positive result on urine toxicological screening and the identification of conditions that could render their participation inappropriate. These included Obsessive-Compulsive Disorder (OCD), Attention Deficit Hyperactivity Disorder (ADHD), and dyslexia. In terms of exclusion criteria, a diagnosis of OCD and ADHD predisposes those individuals to deficits in sustained attention, which is a crucial component to the successful completion of the proposed neurocognitive test battery (Montgomery et al., 2010). In addition to this, individuals with either OCD or ADHD, are clinical populations referred to as neuro-atypical, meaning that in terms of neurological architecture and functioning they differ from the general population. Thus, cognitive performance and cerebral blood flow scores might not be generalisable (Oner et al., 2010). Concerning courses of treatment, these disorders frequently lead to the use of medications impact on neurocognitive performance. Dyslexia was an exclusion criterion for the study as one of the critical tests (Semantic associations) requires a participant to be able to read words.

Consequently, a dyslexia diagnosis would create a statistical confound inhibiting the ability to successfully navigate such tasks (Stoodly & Stein, 2013). Application of these inclusion and exclusion criteria apply to all new empirical findings reported throughout subsequent chapters of this thesis. Furthermore, the researcher made an '*a Priori*' decision to include a cut off of three exposures to any other drug for all three groups (Voluse et al., 2012). For statistical power, an initial "*a priori"* calculation indicated that 66 participants were required for a power level at 0.85 for large effects (f^2 = 0.40), with three independent variables (predictors) and a conventional alpha level of $P < .05$ (Faul & Erdfelder, 1992).

Data Collection Instruments and Protocols

Background Measures

Drug use questionnaire

Background drug use questionnaires provided the researcher with indices of drug use patterns and other lifestyle variables. In this questionnaire, comprehensive details of alcohol and cannabis use, as well as other illicit drug use, are requested, such as first and last drug use, patterns of drug use, frequencies and doses over time. Total lifetime drug and drug use for the past thirty days used calculations used a method employed by (Montgomery, Fisk, Newcombe & Murphy, 2005).

Epworth sleepiness scale (ESS, Johns 1991)

The Epworth Sleepiness Scale (ESS, Johns, 1991), explores the chances of dozing or falling asleep in various situations. A high total score on this scale is indicative of increased subjective daytime sleepiness.

Barrat Behavioural impulsivity scale

The Barrat Behavioural impulsivity scale (Barrat & Patton, 1983) is a widely used measure of impulsiveness. The test measure included first-order factors; attention, motor, self-control, cognitive complexity, perseverance, and mental instability impulsiveness, and second-order factors; attentional, motor, and non-planning impulsiveness

The Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS: Snaith, 2003) measures the levels of anxiety and depression that a person is experiencing. The HADS is a fourteen item scale that generates ordinal data. Seven of the items relate to anxiety and seven relate to depression, with respective dependent variables consequently being generated. Higher scores indicate higher levels of anxiety and depression, respectively.

National Adult Reading Test

The National Adult Reading Test (NART: Nelson & Willison, 2011) is a widely accepted and commonly used method in clinical settings for estimating premorbid intelligence. The test comprises 50 written words in British English which all have irregular spellings (e.g. "aisle"), to test the participant's vocabulary rather than their ability to apply regular pronunciation rules.

Ravens Progressive Matrices (Raven, Raven, & Court, 2004)

This measure is as an indicator of fluid intelligence; it involves a series of problems (5 sets of 12, 60 in total), presented as a symbolic sequence. Participants are required to select an appropriate response to complete the series from a choice of six options. Successful completion of the task requires an understanding of the sequence stimuli and their interaction with one

another. Each block of twelve problems begins with an intuitively simple issue, and the questions become progressively more difficult as the task continues.

Urine sampling protocol

Participants provided a urine sample at the end of the experimental session, in a nearby toilet facility within the Psychology department. The toxicological test screened for the presence of metabolites of both alcohol and cannabis. Participants collected their sample by urinating into a plastic specimen tube, secured by a screw cap. A watertight sealable plastic wallet stored the urine. For the collection of urine, the research operated following the Human Tissue Act (HTA regulations and EHU Quality Manual version 2.0 4.4.3 and 4.8.3) for handling urine.

Standard urine analysis test card sensitive to the presence of metabolites of; Alcohol, Heroin, Opiates, Cannabis, Cocaine, ecstasy (Home Health UK Ltd, Bushey, Herefordshire, UK). If alcohol and or cannabis were present, a red bar appeared in the corresponding box on the probe.

Procedure

Participants completed the Montgomery et al. (2005) drug questionnaire and returned the information to the researcher via e-mail. Once the researcher was able to assess initial suitability for participation, the study required eligible participants to attend one laboratory session. Administration of tests was in the order in which they appear in chapters six and seven. Participants responses determined group allocation; control or either of the experimental groups.

Urine samples were collected and stored for analysis following participant testing. Participants sat in front of a PC loaded with the inquisit programme and related neurocognitive programmes. The researcher fitted the participants with the fNIRS cap; they then watched a 2-minute nature documentary to provided a haematological baseline for the tests. Following this, participants completed the neurocognitive test battery. Results form the basis of the subsequent chapters of the thesis are not discussed further in this chapter. During the performance of the task, fNIRS measured cortical activity. More specifically, the regions of interest for NIRS involved the placement of channels over areas of the left and right dorsolateral/medial

prefrontal cortex. At the same time, participants completed the battery of neuropsychological tests outlined previously. Chapter seven covered the use of fNIRS.

Participants then provided a hair sample for toxicological screening beyond the scope of the current thesis. Hair samples offered a more detailed toxicological history of each participant. Hair analysis would provide information related to the levels of alcohol, THC and CBD present in the body over one month per 1 cm of hair. However, owing to resource and licencing issues related to the legal storage of THC and CBD samples to serve as a comparative marker, such analyses might not be available for inclusion in the present thesis. As this proved to be the case, it is not possible to report further about these samples. The samples will still be able to provide a basis for further analyses beyond the scope of the thesis.

Ethical considerations

The study followed the British Psychological Society's (BPS) Code of Ethics and Conduct (The British Psychological Society [BPS], 2009). Code of Human Research Ethics (BPS, 2014) and the National Institute for Alcohol and Addiction (NIAAA) (2018) and data protection act (2019) guidelines for data storage. A filing cabinet inside a research office held all the data (which is locked when not in use) or on a password protected computers, laptops and USB drives. Before testing all participants were made aware of the fact that they will provide a hair and urine sample. That the testing will take place on an individual basis (i.e. no other participants in the room) and that the assessment involved the use of the NIRS device. Participants were made aware that they were free to withdraw at any point; they did not need to continue. For the time that they have participated in, the researcher awarded a monetary or course credit.

Furthermore, participants were able to withdraw any of their data for up to two weeks following participations. Since the study involved the procurement, and processing of human urine, and saliva, it falls within the remit of the Human Tissue Act 2004. To comply with the relevant guidelines, the primary researcher undertook all appropriate HTA training before the start of the study and followed all guidelines for obtaining consent, handling, transfer and disposal of relevant biological material.

The issue of informed and valid consent from research participants is central to the human tissue act. To comply with the requirements outlined within the EHU Quality Manual Version 20: 4.3.3- Consent Requirements, the present research took into account the following. Before the administration of tests, the participants gave written and valid permission through a standardised consent form. In line with principles of good practice, the consent form was generic (i.e. it refers to the provision and analysis of tissues in a non-specific way that does not necessitate seeking future consent). Participants have the right to withdraw their samples from the study at any time.

The study gave ethical consideration to the fact that participants may construe the results as a justification for taking specific strains of cannabis, consent and information forms accounted for this. They stated that the researcher and the associated agencies in the study do not condone the use of cannabis or the abuse of alcohol, and this research should not be considered an endorsement of substance abuse.

Given that the target population may have some form of cognitive dysfunction, there was a possible discrepancy between the skills needed for adequate consent to the research and the information literature provided by the research team. It was essential to produce participant consent, research information and health literature that was comprehensible at low literacy levels. The researcher proposes that the readability of any literature provided is to be determined by systematic formulae. Readability formulae assigned a numeric value to the readability of written information. The Gunning FOG (Frequency of Gobbledygook) index, Flesch-Kincaid Grade Level (FK), SMOG (Simple Measure of Gobbledygook) formula and Flesch Reading Ease (FRE) scale are functions of the number of characters, syllables, words or sentences in a text sample and extensively to measure the readability of health information. The notion of being able to calculate the readability of the text is so widely accepted that word-processing software packages, such as Microsoft Word, include readability tests. The FOG, SMOG and F-K tests provide estimates of the number of years of education required to understand a passage of text. Thus, all written information given to the participants had to be processed by one of these readability measures before dissemination. In this instance, the SMOG test to ascertained the readability of the participant information sheet and consent form. A minimum score of 6 and a maximum score of 240 required, the current documents recorded

a score of 18.77 which indicates the documents were suitable to be read by individuals of 13 years of age and above, and as such well within acceptable parameters of readability for the target population.

It was made clear to the participant that the cognitive functioning scores obtained did not in any way constitute a clinical diagnosis, and that if they did have concerns about their cognitive functioning, they should contact a medical professional. The researcher followed the data protection act 1998 guidelines for electronic data was storage following the requirements of the Data Protection Act 1998. The ultimate responsibility of the disposal of the hard copy records belonged with EHU, and specifically with the principal researcher.

Analytic Strategy

Preliminary data analysis began with the calculation of means and standard deviations for demographic, psychological and substance misuse variables, the removal of outliers was achieved through calculation of Skewness and Kurtosis values and deletion of Z-scores more than ± 3.29. The normalisation of remaining scores required Square, square roots, natural log ($\log_n$), and inverse transformations. Homogeneity of variance and covariance assessed the robustness of the data for MANOVA through Levene's *F* and Box's *M* (Tabachnick and Fidell. 2014). Nonparametric ANOVA (Kruskal-Wallis *H* test) and subsequent Mann-Whitney *U* tests were conducted, with spearman's Rho correlations where appropriate. The homogeneity of variance demonstrated in the ANOVAs was assessed through the F_{max} procedure as described by Tabachnick and Fidell. ANOVA's with subsequent post hoc pairwise comparisons which were two-tailed against Bonferroni adjusted alpha levels of $\alpha' = 0.17$. The relationships between the background variables and variables recording the consumption of alcohol and cannabis using bivariate correlations. Once again, these analyses comprised either parametric or nonparametric correlations, subject to the distribution of the variables in question.

Results

Background Variables

Preliminary analysis of demographic variables indicates a bias towards male participation in the study, making up 72% (*N* = 51) of the total sample, whilst subsequently, females made up 27% (*N* = 19). In terms of the group, allocation results indicate that there is a numerical bias towards males engaging in substance misuse (*N* = 14) for males in the HSD and (*N* = 21) for the HSDCC group, compared with *(N* = 6) and (*N* = 1) for, females respectively). Control group allocation, while still biased towards males (*N* = 16) was more balanced with regards to the number of females (*N* = 12). Chi-Square analysis indicated that there is indeed a statistically significant association between group membership and gender ($\chi 2$ [2, *N* = 70] = 9.26, *P* = .010).

The analysis of background data also indicated that there was no significant difference in age between male participants (*M* = 21.18 years, *SD* = 4.2 years) and female participants (*M* = 22.49 years, *SD* = 2.58 years) in this study (*U* = 453.5, ns). In terms of group allocation and age, HSD'S were older on average (*M* = 22.55 years, *SD* = 5.57 years) than participants in the control (*M* = 21.32 years, *SD* = 4.43 years) and Poly Drug using groups (*M* = 21.53 years, *SD* = 4.68 years). Kruskal Wallis analysis indicated that this difference was not significant (*H* [2, *N* = 70] =1.530, ns.).

Table 5 summarises the psychological and background measures, ANOVA revealed a statistically significant between group's effect for levels of Depression, Premorbid IQ and fluid intelligence. *Post hoc* pairwise comparisons found that higher levels of depression observed in the HSDCC group were statistically significant when compared to both HSD and Controls. However, the differences between controls and HSD were not Significant. HSDCC participants also reported significantly higher premorbid IQ when compared to both HSD and control participants, as well as significantly higher fluid IQ scores compared to the HSD group, but not the controls.

Nonparametric ANOVA (Kruskal Wallis) yielded statistically significant between group's comparisons on impulsivity concerning all six of the Barratt sub-scales. Post hoc Mann

Whitney U tests showed that none of the HSD versus HSDCC comparisons was significant. However, the HSDCC group were significantly higher than the CO group on all of the impulsivity sub-scales except for cognitive complexity. The HSD group had significantly higher scores than the CO group on the cognitive complexity and perseverance sub-scales.

Table 5*:* Mean and Standard deviations for Demographic Variables

Variable	Controls (CO) *N* = 28 Mean (SD)	Heavy social drinkers (HSD) *N* = 20 Mean (SD)	Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22 Mean (SD)	Significance	*Post-hoc*[1] *(1) Controls vs HSD (2) Controls vs HSDCC (3) HSD vs HSDCC*
ESS	3.64 (2.13)	5.30 (9.38)	3.59 (1.56)	*H* [2,*N*=70] = 1.847, *ns*	All *n.s*
HADSD	2.78 (1.72)	2.00 (2.44)	4.72 (1.31)	*F* (2,67)=12.30, *P* <.000, *ηp²=.269*	1. *n.s* 2. *P* <.000 3. *P* <.000
HADSA	2.92 (2.53)	2.92 (2.16)	3.27 (2.16)	*F* (2, 67) =.302, *ns,*	*1. n.s* *2. n.s* 3. *n.s*
Barratts Impulsivity: Attention Subscale	7.50 (0.61)	7.80 (0.61)	8.81 (0.89)	*H* [2, *N*=70] = 11.309, *P* = .004	*1. n.s* 2. *P=.002* 3. *n.s*
Barratts Impulsivity Motor Subscale	15.50 (0.89)	15.90 (0.55)	16.31 (0.89)	*H* [2,*N*=70] = 11.895, *P* = .003	1. *n.s* 2. *P*=.002 3. *n.s*
Barratts Impulsivity Self-control	49.64 (4.07)	51.60 (3.31)	53.72 (4.43)	*H* [2, *N* =70] = 11.719, *P* = .003	1. *n.s* 2. *P*=.002 3. *n.s*
Barratts Impulsivity Cognitive Complexity	5.32 (.475)	5.80 (.410)	5.63 (.492)	*H* [2, *N* = 70] = 11.479, *P* = .003	1. *P* =.001 *2. n.s* *3. n.s*
Barratts Impulsivity Perseverance	5.32 (.475)	5.80 (.410)	5.63 (.492)	*H* [2, *N* =70] = 13.466, *P* = .001	1. *P*=.001 2. *P*=.005 *3. n.s*
Barratts Impulsivity Cognitive Instability	5.25 (.440)	5.40 (.502)	5.72 (.455)	*H* [2, *N* =70] = 11.417, *P* = .003	1. *n.s* 2. *P*=.001 *3. n.s*
NART	105.89 (10.97)	104.55 (14.31)	108.55 (14.36)	*F* (2, 67) = 4.267, *P* = .018, *ηp²=.113*	1. *n.s* 2. *P*=.016 3. *P*=.011
Ravens Progressive Matrices	43.46 (4.45)	40.75 (3.56)	43.86 (3.49)	*F* (2,67) = 3.932, *P* = .024, ηp²=.105	1. *n.s* 2. *n.s* 3. *P*=.013

[1] All *Post-Hoc* analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .017$

Alcohol and Cannabis Consumption

Table 6 reports upon means and standard deviations for alcohol and cannabis indices, inter-group comparisons are, of course, not appropriate for the cannabis consumption variables. The range for the number of hours since the last reported use of cannabis was from 10 hours to 70 hours. Onset age for alcohol use did not differ between the groups. The CO group drank alcohol less frequently than the other two groups for all the timeframes reported. However, CO participants had used alcohol more recently before testing than participants in the other two groups. Concerning estimated units of alcohol consumption, the CO group consumed less than both other groups over the previous six months. However, the number of reported units consumed within a drinking session did not differ significantly between groups.

Table 6: Mean and Standard deviations for Alcohol and cannabis misuse indices

Variable	Controls (CO) *N*= 28	Heavy social drinkers (HSD) *N* = 20	Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22	Significance	*Post-hoc*[1] *(1)Controls vs HSD (2)Controls vs HSDCC (3)HSD vs HSDCC*
Alcohol use frequency in the past three months (median ratings)[2]	2.00	4.00	4.00	*H* [2, *N* = 70] = 54.466, *P* <.000	*1.* *P* <.000 *2.* *P* <.000 *3.* *n.s.*
Age of first use of alcohol (years)	17.12 (4.09)	18.85 (5.53)	16.14 (4.81)	*H* [2, *N* = 70] = 4.69, *ns.*	All *n.s.*
Hours since last alcoholic drink	17.07 (14.3)	37.70 (12.17)	40.45 (15.35)	*F* (2,67) = 17.943, *P* = .001, ηp^2=*.349*	1. *P* <.000 2. *P* <.000 3. *n.s*
Days since last alcoholic drink	.714 (.599)	1.35 (.489)	1.73 (.767)	*F* (2,67) = 16.554, *P* <.000, ηp^2=*.331*	1. *P* .001 2. *P* <.000 *3.* *n.s*
Average Alcohol units Per session	11.54 (9.18)	12.25 (4.75)	9.91 (8.37)	*F* < 1	All *n.s.*
Times drinking per week	1.19 (1.11)	3.20 (1.05)	2.68 (.779)	*F* (2, 66) = 26.364, *P* <.000, ηp^2=*.444*	*1.* *P* < .000 *2.* *P* <.000 *3.* *n.s*
Times drinking per month	4.67 (4.29)	12.80 (422)	10.72 (3.11)	*F* (2,67) = 28.192, *P* <.000, ηp^2=*.457*	*1.* *P* <.000 *2.* *P* <.000 *3.* *n.s*
Times drinking per year	59.69 (56.22)	149.40 (46.49)	123.63 (33.55)	*H* [2, *N* = 70] = 25.951, *P* <.000	*1.* *P* <.000 *2.* *P* <.000 *3.* *n.s*

Alcohol consumed the last six months (units)	36.0 (32.38)	72.0 (20.7)	61.84 (16.60)	F (2,67) = 13.359, P < .000, ηp^2=.258	1. P < .000 2. P = .001 3. n.s
Age of first cannabis use (Years: Mean (*SD*))	-	-	19.46 (4.17)	-	-
Cannabis use in the past three months	-	-	61.0 (58.15)	-	-
Hours since last smoking cannabis	-	-	27.36 (12.52)	-	-
Days since last smoking cannabis	-	-	1.50 (1.99)	-	-
Cannabis consumed in the past six months	-	-	122.00 (116.3)	-	-

[1] All *post-hoc* analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .017$

[2] Rating scale data: 1 = Never, 2 = occasionally, 3 = Frequently, 4 = Always.

Bivariate correlations with covariates representing alcohol consumption showed that the depression scores were on the borderline of a significant negative correlation with the estimated number of alcohol units consumed in the previous six months (r_s (70) = -.234, P = .051, two-tailed). Still, they showed a stronger positive correlation with the number of hours since last alcohol use (r_s (70) = .398, P = .001, two-tailed). Onset age for alcohol use had a positive correlation with the anxiety scores, which, whilst significant, was not strong (r_s (70) = .237, P = .048, two-tailed). Cannabis consumption in the previous 6 months showed a very strong correlation with depression scores (r_s (70) = .538, P < .000, two-tailed). Within the HSDCC group, there was no correlation between the number of hours since last cannabis use and depression scores. Table 7 shows the correlations between the impulsivity sub-scales and measures of alcohol consumption. The estimated alcohol use in the past six months (measured in units of alcohol) and hours since last alcohol consumption showed universally positive correlations with the impulsivity sub-scales. Impulsivity and longer periods of abstinence were correlated to higher consumption as were to impulsivity. The scores for onset age for alcohol use correlated with the "cognitive instability" sub-scale, with this relationship being negative, higher levels of "cognitive instability" correlated to earlier onset age.

Within the HSDCC group (N = 22), no correlation with the age of first cannabis with their scores for depression, anxiety, any of the impulsivity sub-scales, premorbid IQ, or Raven's Matrices scores. However, the number of hours since the last use of cannabis had a relatively strong positive correlation with anxiety scores (r_s (22) = .585, P = .004, two-tailed), indicating that anxiety was higher with longer periods of abstinence. There was no correlation between the duration of cannabis abstinence and any of the other background variables or substance consumption variables. The statistical power of the correlations with these two measures of cannabis is affected by the relatively small number of data points. However, taking values of '0' for cannabis consumption in the CO and HSD groups, estimated cannabis consumed in the previous 6 months did show significant positive correlations with the impulsivity sub-scales for attention (r_s (70) = .362, P = .002, two-tailed), motor performance (r_s (70) = .346, P = .003, two-tailed), self-control (r_s (70) = .349, P = .003, two-tailed), and cognitive instability (r_s (70) = .389, P = .001, two-tailed). Consequently, for both alcohol, cannabis and impulsivity were correlated with higher consumption levels.

Table 7: Spearman correlations between the impulsivity sub-scales and measures of alcohol use[1]

Impulsivity Sub-Scale	Alcohol units consumed in the past six months (N = 70)	Onset age for alcohol use (years) (N = 69)	Hours since last alcohol use (N = 70)
Barratts Impulsivity: Attention Subscale	r_s = .322, P = .007	r_s = -.138, *ns.*	r_s = .340, P = .004
Barratts Impulsivity: Motor Subscale	r_s = .299, P = .012	r_s = -.116, *ns.*	r_s = .398, P = .001
Barratts Impulsivity: Self-control	r_s = .315, P = .008	r_s = -.124, *ns.*	r_s = .379, P = .001
Barratts Impulsivity: Cognitive Complexity	r_s = .364, P = .002	r_s = -.014, *ns.*	r_s = .419, P < .000
Barratts Impulsivity: Perseverance	r_s = .375, P = .001	r_s = -.058, *ns.*	r_s = .421, P < .000
Barratts Impulsivity: Cognitive Instability	r_s = .296, P = .013	r_s = -.265, P = .027	r_s = .374, P = .001

[1] All probability values are two-tailed.

Discussion

This chapter aimed to analyse the background measures for the sample of participants used in this thesis concerning demographic and other background variables, and also the consumption of alcohol and cannabis. The results indicated the variables which are potential covariates with the ability to confound the results for performance on tests of psychological functioning. Although an opportunity sample reported upon here, the predominance of males in the sample

does reflect the findings of more extensive population studies of problematic alcohol use and cannabis use (Tu & Ratner, 2009; Webb, 2007). Nevertheless, some conclusions of the current literature do suggest that parity between genders concerning HSD (Balodis et al., 2009) and cannabis consumption (Hamilton et al., 2019).

Concerning the psychometric measures reported, the HSDCC group showed higher scores for depression than both of the other two groups, whilst depression showed a positive correlation with the level of cannabis consumption in the previous six months. The results are consistent with the existing literature concerning depression related to alcohol use and cannabis consumption (Boden & Fergusson, 2011; Green & Ritter, 2000). The present results also indicate that levels of impulsivity were more considerable in both substance misuse groups, although these were not significantly different from each other. These findings are not surprising when considered with the gender distribution within the sample.

The role of impulsivity in explaining Polydrug use is far from a simple one. Impulsivity is not a homogenous construct but instead consists of several dimensions (Meda et al., 2009). Table 6 notes that the sub-scales for impulsivity show the CO group are significantly lower than either one or both of the other two groups, the distribution of these differences does vary across the sub-scales. These dimensions are a vital feature in the development of some psychiatric conditions, including substance misuse (Makillop & Mattson, 2007).

Impulsivity is related to maintenance of substance misuse (Dawe & Loxton, 2004; Kollins, 2003; Miller et al., 2003). With reward sensitivity resulting in greater attentional impulsivity to alcohol and cannabis-related cues. Chapter 6 of this thesis will examine differences in executive inhibition between the three participant groups, and the relationship between impulsivity and executive inhibition will be a question to be explored.

In terms of Alcohol consumption, the present results indicate that the CO group consumed alcohol less frequently on average than participants in the other two groups. However, within any particular drinking episode, the level of self-reported consumption of units of alcohol does

not seem to differ. Whilst the onset age for alcohol use did not differ significantly between the participant groups; it did show a positive correlation with anxiety which might seem to contradict earlier findings of a relationship with psychosocial adjustment difficulties (Falk et al., 2014). However, results may see the negative correlation in the current data between onset age and the "cognitive instability" sub-scale for as more consistent with such problems, and with the potential disruption to the development of some neural circuitry (Nguyen-Louie et al., 2018; Weissman et al., 2015). Cannabis may require up to 95 days to leave the body, with its lipophilic nature facilitating its retention in bodily tissues (Verstraete, 2004). Thus, making the imposition of a sufficient washout period for cannabis highly problematic, particularly in the context of rising levels of Δ9-THC in black market supplies since the year 2000, which have contributed to making the drug more dependence producing (Freeman et al., 2014; Hardwick & King, 2008; Murphy, 2018). In response to the potentially confounding effect of recent cannabis use on the results throughout this thesis, the study will look at the relationship between time since last cannabis use to other variables which have shown significant inter-group effects. The choice of these variables is explained further in the Analytic Strategy sub-section of Chapter 6. Also, the lack of reported nicotine use by participants is conspicuous and warrants discussion. One interpretation of nicotines absence is the possible confusion shown by participants over the nicotine questions in the drugs questionnaire. Specifically, it is reasonable to assume that the participants may have accepted that the study included estimates of nicotine use is the measure of cannabis cigarette consumption as they also include tobacco as a base substance (Agrawal et al., 2012).

Chapter 6.

Executive Functions and Working Memory: Tasks Used in this Thesis

Introduction

Executive functioning (EF) is a generic term encompassing a series of cognitive processes that exert top-down regulation of working memory (WM) functions to support flexible and adaptive goal-directed behaviour (Alvarez and Emory, 2006). Miyake et al.'s (2000) latent variable analysis revealed three distinct, yet related executive functions: "updating," "inhibition" and "shifting." The updating is part of WM and relates to the ability to maintain information within memory for quick retrieval, along with the ability to shield this information from distraction. Inhibition refers to the ability to deliberately inhibit or override dominant, automatic, or pre-potent responses. Shifting is the ability to switch between multiple tasks, operations, or mental sets. Hofmann et al. (2012) argue that self-regulatory processes are sub-served by executive functions and enable effective goal-directed behaviour. Research from within the psychological literature has argued the EF serves as top-down control mechanisms for the control of WM, which in turn is a cognitive system with a limited capacity that is responsible for temporarily holding information available for processing. WM is essential for reasoning and the guidance of decision-making and behaviour and includes two distinct domains, these being visuospatial working memory (VSWM) and verbal working memory (VWM) (Diamond et al. 2013). VSWM is essential for the manipulation of visual and spatial information, while VWM is responsible for the manipulation of oral and written sound and language processing (Malenka et al. 2009).

It has been reported in the broader academic literature that the application of WM and EF tasks in the assessment of substance misuse has established a pattern of inconsistent results (Cubillo et al., 2014). For example, Waring et al. (2000) reported a highly significant correlation between ecstasy misuse and deficits to WM and EF. However, Nulsen et al. (2010) noted a contradictory pattern with a similar substance misuse group. In an attempt to explain the indeterminate results reported, Mehler et al., (2012) highlighted that inconsistency within the methodologies constituted a significant cause. Specifically, the author argued that this pattern of results was in part due to inconsistencies in the selection of appropriate neurocognitive test measures. The paper concluded that not all tests available to researchers were sufficiently sensitive to the subtle alterations to task performance often seen in substance misuse research.

This line of argument has been supported by Possin (2010), who noted that traditional neurocognitive batteries such as the PASSAT are insufficient for the accurate recording of impairment in the field of substance misuse. An analysis of the PASSAT found that there was an average of 12% overlap between cognitive domains tested. In particular, the author noted how aspects of the IC task overlapped with VSWM. In addition to this, Polderman et al., (2009) indicated that other test batteries such as the Stroop task required access to semantic long term memory. As a consequence, the tests were deemed inappropriate for assessment of neurocognitive impairments for people with an IQ above 100. Gauvin et al. (2016) suggested that in the future researchers must identify as a battery of tests that are sufficiently sensitive to meet the needs of substance misuse research.

While test sensitivity is a salient issue in the field of substance misuse, the need for a robust battery of tests become all the more critical in matters of polydrug use (Parrot et al., 2000). Issues arise from the pharmacological effects that psychoactive agents have on each other and upon attendant neurological structures so that the combined use of multiple substances adds to the complexity of the research. These issues also represent a methodological confound that less robust tests may not be adequate to address (Snyder et al., 2017).

There is as of yet no established battery of tests designed specifically for the assessment of substance misuse. However, the notion that they need to be sufficiently sensitive to detect subtle alterations to and mitigate the potential access to additional cognitive resources has led to a series of tests identified as best suited to this task. Specifically, van Holst et al., (2011) noted that computerised versions of the following functions are the most eligible candidates for a battery of tests suitable for the accurate analysis of substance misuse: Go/No-Go Task, Number Series Task, N-Back Task, Controlled Oral Word Association Test (COWAT), Corsi-Block Tapping Test and the Wisconsin Card Sorting Task (WCST).

Executive Updating

Evidence from within the academic literature has demonstrated executive updating (EU) is particularly vulnerable to the neurotoxic effects of HSD and cannabis consumption. The most frequently used task to assess EU in both HSD and cannabis smoking populations in the N-Back Task. Conventional N-Back measures involve subjects observing a sequence of stimuli. The test consists of indicating when the current letter matches the one from "*n"* steps earlier in the series Gazzaniga et al. (2009).

The N-Back task has been well cited in the academic literature and has been able to demonstrate EU task impairment in HSD populations. For example, Courtney and Polich (2009) reported a statistically significant difference between HSD and control populations with regards to EU performance, with results indicating that the HSD group showed significant reductions in all indices of task performance when analysed via the N-Back paradigm. The N-Back task has also demonstrated impairment to EU in cannabis smoking populations. For example, Cousjin et al. (2014) reported that when comparing the N-Back task performance of heavy cannabis smokers (N = 32) to non-smoking controls (N = 41), the cannabis smokers reported significantly lower outcomes on all N-back conditions in comparison to the control group. The authors concluded from these results that heavy cannabis users require more significant effort to complete the N-Back task, which is indicative of impairment to this executive domain

Inhibitory Control

Substance misuse research has also demonstrated that inhibitory control (IC) is vulnerable to the neurotoxic effects of HSD and Cannabis consumption. The most frequently used task to assess inhibitory control (IC) in both HSD and cannabis smoking populations in the Go/ No-Go test (Schmidt et al., 2017). The Go/No-Go test requires participants to inhibit their responses to stimuli actively. Participants respond to "go" (Green box) stimuli by clicking button or space bar on computerised versions and actively inhibit this by making no response for "no-go"(Blue box stimuli). The Go/No Go has been well cited in the academic literature and has been able to demonstrate IC task impairment in HSD populations. For example, Mullan et al. (2011) compared IC task performance via the Go/No-Go test in (N = 40) HSD participants aged between 30 and 45 years who engaged in HSD behaviours for more than twenty years, to that of (N = 50) moderate drinkers and (N = 74) alcohol abstinence controls matched by age. One way ANOVA indicated a significant difference between HSD and control participants,

with the HSD participants performing worse on all measures of the test. The authors concluded that inhibitory control plays a significant role in the translation of intent to engage in HSD into active engagement in the act.

The Go/No-Go task has also demonstrated impairment to IC in cannabis smoking populations. For example, Battisti et al. (2010) found that upon a comparison of 21 cannabis users with a mean 16.4 years of daily use to 19 non using controls, cannabis users performed worse on the Stroop task. Expressly, once controlling for potentially confounding influences arising from the use of additional substances such as alcohol and MDMA, the results indicated that cannabis smokers reported more significant numbers of errors. Age of onset of cannabis use is a crucial predictor for task performance, with early-onset with enhanced task impairment.

Executive Set Shifting

The Wisconsin Card Sorting Test (WCST) cited within the academic literature on executive functioning regarded as being one of the most robust and frequently used measures of executive set-shifting (ESS) within the substance misuse literature (Reynolds, 2015). In particular, Diamond et al. (2013) have noted that the most frequently used test in investigations of ESS in both HSD and cannabis consumption studies is the WCST. The WCST requires people to classify cards according to different criteria. There are four different ways to categorise each card, and the only feedback is whether the classification is correct or not, card organisation is through colour, number or the shape of the symbols. The classification rule changes every ten cards, and this implies that once the participant has figured out the criteria, the participant will start making one or more mistakes when the rule changes. The task measures how well people can adapt to the changing rules using, for example, measures of errors and reaction times (Faustino et al., 2019).

Studies which have used the WCST have demonstrated ESS impairment in HSD populations. Such results support the notion that consumption of alcohol consistent with binge drinking criteria is positively associated with impaired cognitive switching tasks in young adults (Montgomery et al. 2012; Bensman et al. 2014). Jurk et al. (2018) reported that in measures that require cognitive control, undergraduate HSD (18-21 years of age) display a tendency to make significantly more errors and display reduced reaction times (RT) when compared to

adults. Furthermore, conflict costs (i.e. RT/error differences between high and low conflict trials) are more pronounced (Crone et al. 2006). These results are indicative of a reduction in the efficiency of the cognitive control system as it pertains to ESS in HSD's.

Deficits to executive switching (ESS) in cannabis consumption studies, were researched by Roberts et al. (2013). Results indicated a significant between groups effect with the cannabis polydrug users displaying greater impairment to ESS comparative to the control group. The study concluded that there was evidence of atypical processing of attentional shifting in the cannabis users. More specifically, research conducted by McHale et al. (2008) was able to demonstrate cannabis consumption resulted in increased error rates and reduced reaction times compared to non-cannabis using controls.

Inductive Reasoning

An additional component of EF, although not included in Myake et al.'s., (2000) original conceptualisation of WM, is inductive reasoning (IR). IR is a method of reasoning in which the premises supply some evidence for the solution to a problem. As discussed below, previous research has identified that both HSD and cannabis consumption impair IR. One of the most frequently used task to assess IR in both HSD and cannabis smoking populations is the Number Series Task (NST). Conventional NST measures involve participants to observe a series of number strings. Participants then identify the pattern that dictates the numbers in the sequence, i.e. increasing in increments of 2 or multiples of 5 etc. (Zhong et al., 2011).

The NST has been well cited in the academic literature and has been able to demonstrate IR task impairment in HSD populations. For example, Weissenborn and Duka. (2003) compared HSD participants (N = 95) to non-HSD controls (N = 90) on measures of decision making and IR. Results indicated that the HSD group performed significantly worse on all measured indices of the NST. The authors concluded that IR measured through the NST was a suitable assessment measure for the assessment of reasoning and decision making in HSD populations and should inform the development of the effective intervention in HSD populations.

The NST has also been used to demonstrate impairment to IR in cannabis smoking populations. For example, in a recent literature review on cannabis consumption and cognitive impairment Crean et al. (2012) noted that there is a severe lack of research within the field of cannabis

consumption and IR. Those studies carried out so far reporting performance impairments in those tasks that load heavily onto pattern recognition such as the NST. Crean and colleagues were able to demonstrate that studies utilising the NST have consistently identified cognitive impairment in moderate, chronic and heavy cannabis users. Their review also notes that these effects are persistent after a period of abstinence.

Visuospatial Working Memory

Research has also highlighted Visuospatial working memory (VSWM) as being particularly vulnerable to both of these substances, and as such, is a suitable candidate for inclusion in this thesis. VSWM draws upon the organisational resources of WM (Miyake et al., 2001), with performance decrements reported which were related to the use of ecstasy (MDMA) (Murphy et al., 2012; Wareing et al., 2004, 2005). However, the role of cannabis concerning these performance decrements was unclear. VSWM is, therefore, a suitable area for the investigation of effects related to heavy social drinking and cannabis. The most frequently used task to assess VSWM in both HSD and cannabis smoking populations is the Corsi Block Tapping Test (CBTT), with computerised variations of this task also having devised. Concerning 'physical' versions of the CBTT, the test involves mimicking a researcher as he/she taps a sequence of up to nine identical spatially separated blocks. The series starts simple, usually using two blocks, but becomes more complex until the subject's performance suffers. This number is known as the Corsi Span, and the average is about 5-6 for participants (Kessells et al., 2000). Computerised adaptations generally involve remembering the sequence with which the constituent cells of a visual matrix light up. By varying the length of the series task difficulty can be controlled (see Wareing et al., 2004, 2005).

A relationship has reported between VSWM impairment in both HSD and cannabis consumption populations. In particular, Calbaria et al. (2017) compared 155 undergraduate students over six years concerning an HSD group and controls. Over the six years, the HSD group consistently committed more errors and showed a lower VSWM span in the difficult blocks than non-drinking controls. Although decrements in VSWM span showed some improvement, perseveration errors remained constant throughout the follow-ups in stable HSD participants. Concerning cannabis consumption, Makella et al. (2006) demonstrated that administration of doses of THC to non-cannabis smoking volunteers resulted in statistically

significant differences to VSWM during the CBBT, with participants showing more intrusion errors during task performance.

Verbal Working Memory

In addition to VSWM, verbal working memory is a component of working memory that is particularly vulnerable to the neurotoxic effects of both HSD and cannabis consumption. The most frequently used task to assess VWM measure access to semantic long term memory (Access). Access memory tasks have demonstrated a particular vulnerability to substance misuse neurotoxicity in both HSD and cannabis smoking populations. The most widely used measure to assess access is the Controlled Oral Word Association Task (COWAT). The test asks the subject to write as many words as possible beginning with the letter 'S' within a 5-minute limit, then as many words as possible beginning with letter 'C' within the 4-minute limit. The total number of 'S' and 'C' words produced, minus the number of rule-breaking and perseverative responses, yield the patients' measure of verbal fluency (Stuss, 1998). The COWAT has been having been able to demonstrate Access task impairment in HSD populations. For example, Parada et al. (2011) compared (N = 62) HSD to (N = 60) non-drinking controls on a battery of neurocognitive test measures including a measure of Access to LTM, through the use of the COWAT. Results indicated that the HSD reported a statistically significant reduction in the Total number of correct words produced across all three test conditions. The authors concluded that the HSD group was demonstrating impairment to Access to LTM. The COWAT has also been used to illustrate impairment to Access task performance in cannabis smoking populations. For example, Murphy et al. (2011) examined the relationship between the consumption of cannabis and performance on the random letter generation task (RLGT). Performance measures compared ecstasy and cannabis polydrug users, (N = 15), to cannabis only users, (N = 13), with both groups compared to controls with no exposure to either drug, (N = 12). Results from a regression model comprising intelligence measures and estimates of ecstasy and cannabis consumption indicated that cannabis consumption contributed to the predicted redundancy scores on the RLGT.

Identified Covariates and Executive Functioning

The covariates identified in chapter five have also demonstrated a correlational relationship with EF task performance in cannabis smoking populations. For example, Moreno et al. (2012) evaluated impulsivity depression and IQ scores in cannabis smokers engaged in EF and WM task performance. Results indicated that the cannabis users (N=26) reported elevated scores for impulsivity and depression, while also displaying demised premorbid and fluid IQ scores.

Evidence from within substance misuse research has also been able to demonstrate a correlational relationship between units of THC and increasing deficits to IC (Murphy et al. 2018). Herzig et al. (2014) were able to identify a significant correlational relationship between the amount of THC consumed and an increase in impairment to EF and WM performance on the Go/No-Go condition and Corsi Block Tapping Test for cannabis users.

Aral et al. (2013) reported that HSD and cannabis smokers recorded elevated levels of depression, diminished premorbid and fluid IQ scores, all of which were associated with deficits to EF task performance in an HSD group. A meta-analysis conducted by Stephan et al. (2017) reported that increased levels of impulsivity resulted in deficiencies in WM an EF. HSD's report greater levels of impulsivity across all six measures of the BIS compared to controls. Increases in impulsivity resulted in decreases in EF task performance. Indices of alcohol use have also correlated with reductions in EF task performance Easdon et al., (2005) reported a positive correlation between units consumed in the past six months, age of onset drinking and an increase in errors reported in HSD's compared to controls.

The measures described in this chapter provided an account of the conceptualisation of both Working Memory and Executive functioning in this study. The chapter provided a conceptualisation of the justification for the selection of measures. The next chapter reports on the administration of these tasks, and the results obtained.

Chapter 7

HSD and cannabis use: implications for Executive Functions and Working memory

Introduction

Following on from the discussion outlined in chapter six, concerning the selection of appropriate cognitive functions tests for polydrug research. This chapter will report upon the administration and analysis of those WM and EF tasks identified as being potentially the most robust with regards to both HSD and cannabis consumption. This analysis aims to ascertain whether HSDCC polydrug use results in more significant neurocognitive impairment than HSD alone.

Methods

Design

This study utilised a 3-participant group design with a control group consisting of non-binging alcohol users (CO) and two experimental groups of binge drinkers (HSD) and binge drinking-cannabis smoking polydrug users (HSDCC). These drug-taking behaviour types served as the independent variable (IV) at three levels (i.e. binge drinker, binge drinking cannabis using polydrug user and light social drinking-illicit drug-naive controls). The results of the cognitive test scores served as the dependant variables (DV). The experiment was a natural using pre-existing groups rather than random allocation of participants to conditions.

Participants

Participant recruitment, inclusion and exclusion criteria are in the Participants sub-section in chapter 5.

Cognitive task Performance Measures.

The Go/ No- Go task.

The cued Go/ No-Go task (Fillmore, 2003) is a measure of executive inhibition, to assess this elicits responses through the presentation of an initial 'Go' or 'No-Go' cue before the presence of the 'Go' or 'No-Go' target. Cues provide information concerning the probability of a Go target

appearing. Manipulation of the cue-target relationship so that the cues have a high probability of correctly signalling a 'Go' or 'No-Go' target (valid cues), and a low probability of incorrectly signalling a target (invalid clues) (see Figure 5). Correct stimuli tend to facilitate response inhibition and speed response execution, whereas incorrect cue cues tend to impair response inhibition and slow response execution (Fillmore & Weafer, 2013).

Figure 6 presents the sequence of stimulus events for a valid 'Go' cue trial: the 'Go' cue is shown at one of the five SOAs, signalling the subject to prepare to respond to the expected 'Go' target. When presented with the 'Go' target, the participant responds by pressing a computer key, and the computer provides feedback regarding the accuracy and speed of the response (Fillmore & Weafer, 2013). In this condition, the valid 'Go' cue allows the subject to prepare to respond to the 'Go' target, so that reaction time to the 'Go' target increases. Figure 7 illustrates the sequence of stimulus events for an invalid 'Go' cue trial: presentation of the 'Go' cue prepares the subject to respond to the expected 'Go' target. When the 'No-Go' mark appears, the participant often fails to inhibit the response, and incorrectly responds to the 'No-Go' target. Poor inhibitory control is evident by more failures to inhibit responses in this condition. A test presents 250 trials and requires 15 minutes to complete. The dependent variables generated by this task which will be analysed here will be Task Completion Time (ms), Error Rate for Vertical Cues, and Error Rate for Horizontal Cues. Analysis of the Psychometric properties of the test indicated that it has strong reliability (r =.098, $P \leq .001$) and validity (.070) measures (Filmore et al., 2003).

Figure 5: Cued Go/No-Go Task

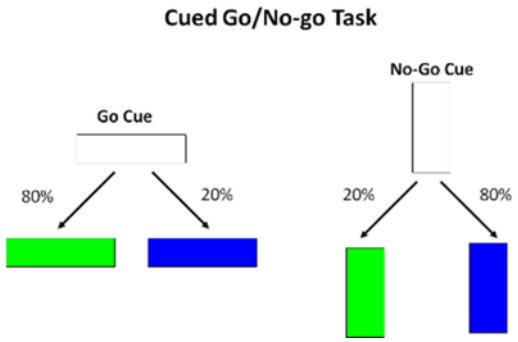


Figure 5 describes the Cue-target combination probabilities on the cued go/no go task. Left panel: go cue precede go target (green box) on 80% of trials (valid go cue condition) and no-go targets (blue boxes) on 20% of trials (invalid go cue condition). Inhibitory failures are most common in the invalid go cue condition. Right panel: no-go cues precede a no-go target (blue boxes) on 80% of trials (valid no-go cue (Screenshot is from the EPBL, 201

Figure 6: Schematic representation of the trial procedure in the valid 'Go' cue condition

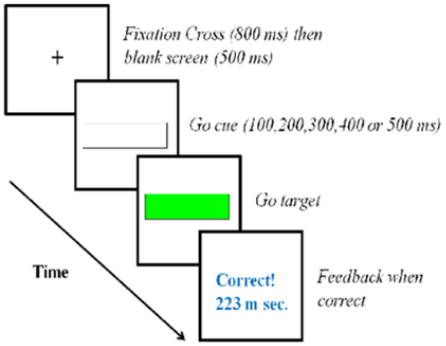


Figure 6. The sequence of stimulus events presented to a participant accompanied by the display duration in milliseconds and a corresponding correct response (*Screenshot taken from the EPBL, 2019*

Figure 7: Schematic representation of the trial procedure in the invalid go cue condition.

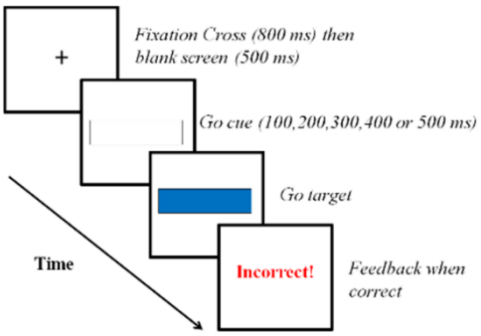


Figure 7. identical to figure 2 concerning the stimulus presentation sequence and duration in milliseconds, this time is displaying the incorrect cue (Screenshot taken from the EPBL, 2019).

Inductive reasoning measure: Number Series Test

In each condition, the participant identifies the pattern that determines the distribution of number scores presented. Participants are then required to use this information to identify the next number in the sequence from a series of options. Once the participant has made their choice via mouse-click, the selection gets briefly highlighted before the subsequent trial starts. Before the start of the test, five practice problems are presented that explain the logic behind the pattern determining the number sequences to ensure that the participants understand the rules of the study. Participants have 4.5 min to complete the test with a clock on the screen that counts down the minutes for the participants. The inductive reasoning test has two dependent variables, these being completion time (ms) and the number of correctly recognised patterns Psychometric analysis has indicated that this measure has robust reliability $r = 0.92$ ($P \leq .005$) and validity (0.88) scores (Preston & Coleman, 2000).

The N-Back Test

The letter N-Back task (Figure 8) displays sequences of uppercase consonants with a stimulus duration of 500 milliseconds and interstimulus levels of 2500 milliseconds. Uppercase consonants maximise readability of stimuli. In the 0 back condition participants responded if the target consonant was identical to the one preceding it. During the one back condition, participants responded if the target consonant was similar to the one presented one trial ago. In the two back condition participants responded if the target consonant was identical to the one-two trials back, in the three back condition participants responded if the target was the same as the letter presented three tests ago. Each condition was repeated three times in a pseudo-random order, for a total of 135 stimuli. A target foul ratio of 2:1 (33%) of all marks is maintained throughout. Participants are informed about an upcoming condition during a nine-second delay between each test. This delay allows the participant to rest and permitted the recovery of haemodynamic response from the previous situation. Total task time was 495 seconds. Psychometric analysis has reported the reliability of the measures as, $r = .094$ ($P \leq .001$), while validity was .80 (De De, 2013).

Figure 8: A trial sequence of the N Back Test

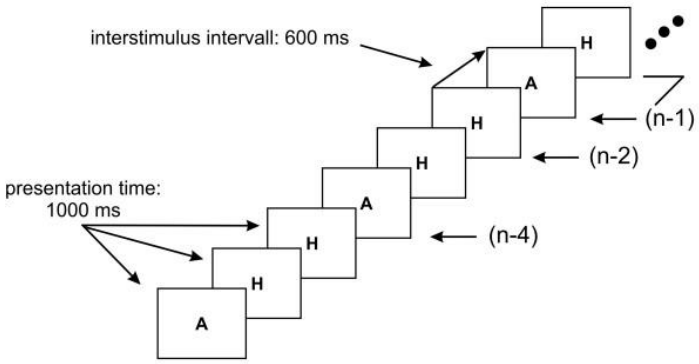


Figure 8 describes the target letter presentation and the N back (1-4) target, the and milliseconds between numbers within the sequence Screenshot taken from the EPBL, 2019.

Semantic Long Term Memory measure

Controlled Oral Word Association Test, abbreviated COWA or COWAT, is a verbal fluency test that measures spontaneous production of words belonging to the same category or beginning with some designated letter. The participant names a word that starts with a letter, excluding proper nouns, for one minute and this procedure repeats three

times. The most commons letters used are FAS because of their frequency in the English language. Task administration requires between 5 and 10 minutes. The Dependent Variables (DV) for this task are completion time (ms), and the total number of words correctly produced Psychometric analysis reported that the COWAT scored r = .084 ($P \leq .001$) for reliability and .087 for validity (Ross et al., 2007).

The Wisconsin Card Sorting Test (WCST)

The WCST (Figure 9) is a neuropsychological test of "set-shifting", i.e. the ability to display flexibility in the face of changing schedules of reinforcement. Participants analyse stimulus cards. The participant is told to match the cards, but not how to compare; however, they know whether a particular match is right or wrong. Psychometric analysis indicated that the measure reported a reliability score of r = .88 ($P \leq .001$) and validity of .90 (Strauss, 2006).

Figure 9: Condition Layout of the computerised WCST

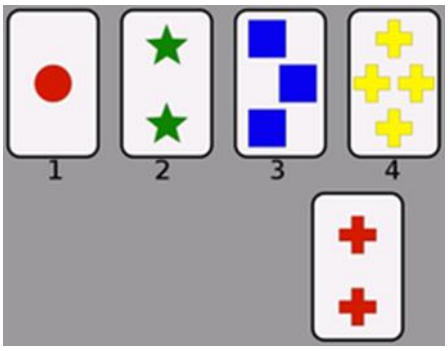


Figure 9 Descries the layout of the computerised WCST; participants use the mouse to click on one of the piles labelled 1 to 4 indicating where the card in the bottom left corner belongs (EPBL, 2019).

Visuospatial Computerised Grid Task.

Based on the traditional (Corsi) block tapping task (Figure 10), the computerised grid task measures of visuospatial working memory involved the participant observing the computer screen, which presents an image of nine equally spaced blocks. These blocks are "lit up" by the computer, turning from blue to yellow. Once the end of the sequence is reached, the squares reset, the participant is then required to repeat the series back in order by using the mouse to click on the Blocks in the order that they changed colour. The sequence starts simple, comprising two blocks, but becomes more complex until the subject's performance suffers. This number is known as the visuospatial span and averages about 5 for normal human subjects.

The test measures both the number of correct sequences and the most extended sequence remembered. Psychometric analysis indicated that the task had a reliability score of r =.89 (P ≤.001) and a validity score of .90 (Robinson & Brewer, 2016).

Figure 10: Screenshot example of the VSWM computerised Grid Task

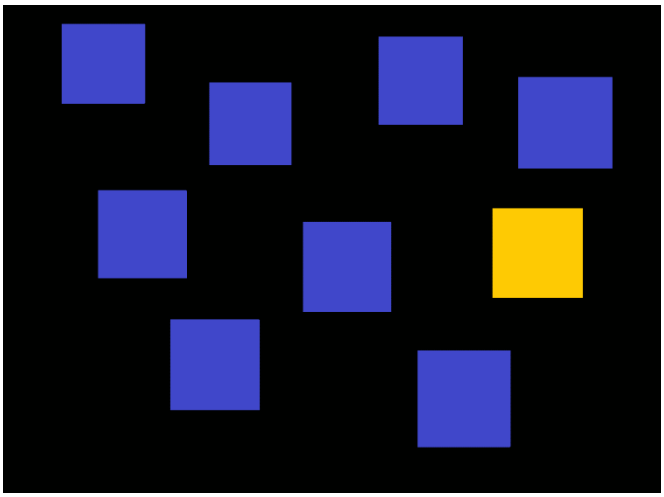


Figure 10 describes the computerised layout of the VSWM Grid Task; participants click on the boxes. In the sequence, they turn yellow[1]. The yellow symbolises the current block in the series (EPBL, 2019).

Procedure

On arrival at the Human Tissue Laboratory in the Department of Psychology, the researcher oversaw the completion of the consent forms and collected samples of urine for toxicology measures. The researcher then briefed the participants as to the procedure. The researcher also collected hair and saliva samples for analysis which fall outside the scope of the present thesis. After this, participants informed about the use of *f*NIRS. The administration of the cognitive tasks scores preceded this. The researchers administered the tasks in the order that they appear in the methods section of this chapter. The administration order was determined automatically by the "inquisit" programme. The researchers decided not to alter the test order, as participants were given an unlimited amount of time to complete the tests, and could have breaks between measures or pause tests at any time. In this way, the study intended to negate any risk of mental fatigue influencing the results. Upon completion of the cognitive functions measures,

Analytic Strategy

The data analysis began with the calculation of means and standard deviations, with the removal of outliers achieved through analysis of skewness and kurtosis values and the deletion

of z-scores exceeding ± 3.29, for all cognitive tasks. The calculation of *Z*-scores was part of the preparation for MANOVA, which accommodated the multiple DVs for tests without compromising alpha levels and inflating the probability of a Type 1 error (Tabachnick & Fidell. 2014). The analysis than employed square, square root, natural log ($\log_n$), and inverse transformations as appropriate to normalise the distribution of scores to satisfy the requirements for MANOVA. Homogeneity of variance and covariance assessed the robustness of the data for MANOVA through Levene's *F*, and Box's *M*.

Data analysis evaluated the univariate results against a revised alpha level calculated by the procedure described by Tabachnick and Fidell (2014 P.312). Where MANOVA was not appropriate due to its assumptions not being met by the data, non-parametric Kruskal-Wallis *H* test and subsequent Mann-Whitney *U* tests were conducted, with correlations where applicable. The analysis evaluated the results of any such tests against Bonferroni adjusted alpha levels of $\alpha' = 0.17$. The relationships between the background variables, consumption of alcohol and cannabis and Behavioural Task performance using bivariate correlations. Once again, these analyses comprised either parametric or non-parametric correlations, subject to the distribution of the variables in question.

Results

Go/No-Go Task Performance

The Go/No-Go task generated nine dependent variables (DVs). These were task completion time; error rate vertical "cues". Error rate horizontal "cues"; error rate for trials in which "cue" the is Vertical, and the target is a go response (EVTG). Reaction time for "trials" in which the "cue" is Vertical, and the target is a no go (EVTN). Reaction time for No Go response; error rate for trials in which the cue was horizontal was a go response (EHTG); overall mean rt (in ms) for target = go, and reaction time for "trials" in which the "cue" was horizontal, and the target was a no go response (EHTN).

Preliminary analysis of the data indicated issues of skewness and kurtosis across all DV's. Subsequent analysis of *Z*-Scores for the DVs had a cut-off score of $Z = \pm 3.29$. These scores indicated no outliers for the following DV's; completion Time, overall means reaction time for the target "go", reaction time for trial in which the cue is vertical, and the target is a go response.

Reaction time for the "trial" in which the "cue" is horizontal and, the target is a go response. However, two outliers with a score of $Z = 4.04$ were identified and removed for the DV Error rate for vertical cues. The error rate for horizontal "cues" also identified two outliers with scores of $Z = 3.32$ and $Z = 4.11$. The error rate for trials in which the "cue" is vertical and the target is a go response highlighted two outliers, with scores of $Z = 3.78$ and $Z = 5.80$. The error rate for trials in which the cue is vertical, and the target is a no go response reported two outliers, with scores of $Z = 3.56$ and $Z = 5.09$. The error rate for No Go Response reported one outlier with a score of $Z = 5.9$. Scores for trials in which the cue was horizontal and the target was a go response had two outliers with scores of $Z = 3.5$ and $Z = 4.8$. While error rate for trials in which the cue was horizontal and the target was a no go response identified two outliers with scores of $Z = 5.36$.

Checks for normality of score distributions for the revised variables following the transformation procedures described in the Analytic Strategy indicated that both mean reaction time (in ms) for trial in which the cue was vertical. Target was going and mean rt (in ms) for trials in which the cue was horizontal, and the target was "go", were both normally distributed. Subsequent *Z*-Score transformations normalised the distribution of the remaining variables. However, this was at the cost of losing data through the number of zero scores, so that these methods could not transform the data, as the *N* values reported here demonstrate. Inverse transformations normalised scores for Error rate vertical, ($N = 37$) and Error rate for horizontal cues ($N = 15$). The error rate for trials in which the cue was vertical, and the target was Go was successfully transformed with ($N = 21$) for Log_n and inverse transformations. Log_n and inverse transformations normalised error rates for the No Go response ($N = 18$). Trials in which the cue was horizontal, and the target was "go" was also successfully transformed via Log_n transformations with an ($N = 25$). Square root transformations of the Error rate for trials in which the cue was vertical and the target was no go reported ($N = 68$), while overall mean reaction time (in ms) for the target go (correct responses only) reported ($N = 70$). Finally, normalization failed for task completion time following attempted transformations.

In summary, the DVs included in the MANOVA were square root transformations of EVTN, and Square root transformations of the overall mean rt (in ms) for target = go (correct responses only). However, the MANOVA results were not valid due to a lack of homogeneity of variance and covariance, as shown by Box' *M* statistic. Due to the high number of DVs, the analysis used an inspection of the inter-group mean differences to select the five DVs with the inter-

group differences, for which the research evaluated nonparametric studies against a Bonferroni adjusted alpha level of $P \leq .01$. Table 8 reports the results for the Go/No Go task. The subsequent non-parametric analysis indicated a statistically significant effect between groups effect for Error Rate for Horizontal Cues and Overall Mean Reaction Time (in ms) for the go responses. Results were evaluated *Post-Hoc* pairwise comparisons against a Bonferroni adjusted alpha level of $P \leq .003$, and showed that the HSDCC group displayed significantly quicker reaction times for 'GO' responses than both the HSD and CO group. There was a marginally significant main effect across groups for the error rate for horizontal cues (evaluated against the Bonferroni adjusted alpha level). Still, none of the inter-group comparisons was significant.

Table 8: Means and (*SD's*) for the Go/ No-Go task response

Variable	**Controls (CO) *N* = 28**	**Heavy social drinkers (HSD) *N* = 20**	**Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22**	**Significance**	***Post-hoc*[1] *1.Control vs HSD 2.Controls vs HSDCC 3.HSD vs HSDCC***
Task Completion Time (ms)	821708.571 (43059.422)	805894.950 (15687.263)	833046.681 (59812.003)	*H [2, N =70] = .774, P = .679*	*1. n.a 2. n.a 3. n.a*
Reaction Time for Go Response	387.90 (37.14)	425.05 (42.38)	351.77 (5.90)	*H [2, N =70] = 32.238, P* = .000	*1. n.s 2. P* ≤ .000 *3. P* ≤ .000
The error rate for Horizontal Cues	.003 (.006)	.004 (.006)	.000 (.000)	*H [2, N =70] = 9.344, P* = .009	*1. n.s 2. n.s 3. n.s*
Error Rate For Vertical Cues	.149 (.589)	.003 (.004)	.731 (1.418)	*H [2, N =70] = 3.187, P* = .203	*1. n.a 2. n.a 3. n.a*
Error Rate For Trials in which cue = Vertical and Target = No Go	011 (.019)	.004 (.006)	.009 (.012)	*H [2, N =70]* =1.292 *P*=.524	*1. n.a 2. n.a 3. n.a*

.

Error Rate For Trials in which cue = Vertical and Target = Go	.082 (.376)	.001 (.003)	.276 (.765)	Omitted From Analysis	*1. n.a* *2. n.a* *3. n.a*
Error Rate for Error Rate for No Go Response	.010 (.017)	.000 (.003)	.004 (.007)	Omitted From Analysis	*1. n.a* *2. n.a* *3. n.a*
Trials in Which Cue = Horizontal and Target = Go	.006 (.009)	.004 (.005)	.004 (.001)	Omitted From Analysis	*1. n.a* *2. n.a* *3. n.a*
Error Rate For Trials in Which Cue = Horizontal and Target = No Go	.008 (.004)	.000 (.000)	.000 (.002)	Omitted From Analysis	*1. n.a* *2. n.a* *3. n.a*

[1] All *Post-Hoc* analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .003$

Number Series Task Performance

The NST generated two DV's, specifically completion time and the total of number patters correctly recognised. The *Z*-scores for skewness and kurtosis indicated the normal distribution of correct pattern recognition scores while completion time was not. The *Z*-score analysis identified two outliers for completion time for which the cut-off point for scores was $Z = \pm 3.29$. None of the transformations made NST completion time was "normally" distributed and suitable for inclusion in MANOVA. Analysis of these two DVs indicated no correlation. Data analysis proceeded with a Univariate analysis without the Bonferroni adjustment for the primary effect size due to the lack of correlation between the variables. *Post Hoc* comparisons still required Bonferroni adjustments, of $\alpha' = P \leq .017$ two-tailed.

Table 9 reports the results for the NST, the univariate analysis indicated a significant main effect across groups for correct pattern recognition, with controls showing better pattern recognition in comparison to the HSD group. No other inter-group comparisons were meaningful for this variable, and there were no significant effects for completion times.

Table 9: Means and (*SDs*) for Number Series Task Performance

Variable	**Controls (CO) *N* = 28**	**Heavy social drinkers (HSD) *N* = 20**	**Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22**	**Significance**	***Post-hoc*[1] *1.Control vs HSD 2.Controls vs HSDCC 3.HSD vs HSDCC***
Correct Pattern Recognition	3.357 (.227)	2.350 (.269)	2.909 (.256)	*F* (2,67) = 4.100, *P* = .01, ηp^2 *=.109*	1.*P* = .006 2. *n.s* *3. n.s*
Time Taken	239153.071 (94372.026)	298760.900 (376072.107)	617482.363 (1027065.754)	*H [2, N =70]* =2.919 *P*=.232	1. *n.a* 2. *n.a* *3. n.a*

1 All Post-Hoc analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .01$

N-Back Task Performance.

0-Back Task Performance

The N-Back Task generated 5 DVs; RTs, % correct responses, False alarms, Misses and Correct rejections. Owing to the continuous nature of the task, these DV's repeated across each of the conditions. For the 0-Back, as with the other tests reported here, the cut-off point for outliers is $Z = \pm 3.29$. Subsequent *Z*- Score analysis failed to identify outliers in any of the DVs. Therefore, only the RTs were deemed suitable for parametric analysis using univariate ANOVA. No significant inter-group effect was observed ($F < 1$). None of the subsequent non-parametric tests performed on the four remaining DVs showed significant inter-group results. For all five analyses comparisons of main effects across the groups employed the Bonferroni adjustment alpha level of $\alpha' = P \leq .01$ (two-tailed). Table 10 summarises the results for the 0-back condition.

Table 10: *Means and (SD's) for the 0-Back Condition task Performance*

Variable	Controls (CO) *N* = 28	Heavy social drinkers (HSD) *N* = 20	Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22	Significance	*Post-hoc*[1] *1.Control vs HSD* *2.Controls vs HSDCC* *3.HSD vs HSDCC*
Reaction Time	529.746 (91.890)	531.698 (150.137)	519.673 (117.191)	*F* (2,67) = .065, *P* = .937, ηp^2 = .002	1. *n.a* 2. *n.a* *3. n.a*
Correct responses,	13.9643 (2.252)	14.050 (1.791)	14.1818 (1.592)	*H [2, N =70]* =.659 *P*=.719	1. *n.a* 2. *n.a* *3. n.a*
False alarms,	714 (1.383)	1.250 (1.618)	.818 (1.468)	*H [2, N =70]* =2.127 *P*=.345	1. *n.a* 2. *n.a* *3. n.a*
Misses	1.6429 (2.497)	1.900 (2.174)	1.500 (2.220)	*H [2, N =70]* =.527 *P*=.768	1. *n.a* 2. *n.a* *3. n.a*
Correct rejections.	27.6786 (3.963)	26.150 (5.018)	26.318 (3.992)	*H [2, N =70]* =4.467 *P*=.107	1. *n.a* 2. *n.a* *3. n.a*

1 All Post-Hoc analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .01$

1-Back Task Performance

Preliminary analysis of the scores for the 1-Back condition highlighted the normal distribution of the correct rejection of raw scores without the removal of outliers RT's normalised following removal of outliers from line one. Subsequent transformations calculations rendered the three remaining DV's normal, with square transformations normalising correct response %, false alarms and misses. Analysis subsequently omitted RT's and scores for misses from the study due to excessive correlations. MANOVA was unable to find a significant intergroup effect (Pillai's Trace $F < 1$), with none of the univariate results approaching significance. Similarly, the non-parametric Kruskal Wallis for RTs and misses failed to find a between-group difference for the remaining DVs. Table 11 summarises the results for the 1-back condition.

Table 11: *Means and (SD's) for the 1-Back Condition task Performance*

Variable	Controls (CO) *N* = 28	Heavy social drinkers (HSD) *N* = 20	Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22	Significance	*Post-hoc*[1] *1.Control vs HSD* *2.Controls vs HSDCC* *3.HSD vs HSDCC*
Reaction Time	564.234 (124.594)	568.726 (85.050)	529.507 (91.373)	*H [2, N =70] =1.553* *P*=.460	1. *n.a* 2. *n.a* *3. n.a*
Correct responses,	10.285 (4.302)	11.000 (3.195)	11.454 (3.173)	*F* (2, 66) = .545, *P* = .528, η_p^2 = .016	1. *n.a* 2. *n.a* *3. n.a*
False alarms,	2.178 (1.764)	2.150 (1.694)	1.4545 (1.765)	*F* (2, 66) = 1.132 *P* = .329, η_p^2 = .033	1. *n.a* 2. *n.a* *3. n.a*
Misses	4.071 (4.233)	3.300 (2.957)	3.454 (2.772)	*H [2, N =70]* =.610 *P*=.737	1. *n.a* 2. *n.a* *3. n.a*
Correct rejections.	28.250 (1.647)	27.600 (1.818)	28.318 (1.492)	*F* (2, 66) = 1.124, *P* = .331, η_p^2 = .033	1. *n.a* 2. *n.a* *3. n.a*

1 All Post-Hoc analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of P ≤ .015

2-Back Task Performance

Scores for the 2-Back condition highlighted that the only normally distributed scores were % correct, whilst removal of outliers from line one normalised the RTs scores. There were no outliers for the other variables. Square root transformations rendered normal the distributions of the false alarms and misses, but not the correct rejections. Further attempts at normalisation for the valid rejection scores failed with both natural log and natural log (In) and therefore could not be used in the MANOVA or any other parametric analysis. Non-parametric Kruskal-Wallis analysis of correct rejections did not show a significant inter-group difference. Consideration of the correlation scores highlighted those correct responses and SQRT miss showing a highly significant negative correlation. The SQRT misses analysis subsequently omitted the variable from the MANOVA due to an excessive correlation with at least one of the other DVs.

The analysis included the DVs of raw scores for % correct responses, RTs (with outlier removed) and square root transformations of false alarms in the MANOVA solution. The results indicated that there was a significant Levene's *F* for the RTs. However, Tabachnick and Fidell (2014) recommend the F_{max} test as more appropriate to Levene's *F* for homogeneity of variance. F_{max} variance calculations indicated that Control group variance = 16,136.7581, HSD variance = 36,989.4441, and HSDCC variance = 21,258.2028. As the ratio of smallest group size and the largest is less than 1:4, the F_{max} test allows a ratio between the smallest variance and the largest of up to 1:10 for homogeneity of variance to be claimed (Tabachnick & Fidell, 2014). The ratio between the smallest and largest variances above is well within this limit. Consequently, MANOVA is, therefore, valid with regards to the homogeneity of variance. The MANOVA result for inter-group effects was significant with Pillai's Trace F (6, 130) = 2.309, P = .038, η_p^2 = .096.

Table 12 reports the scores for the 2-Back condition. The results indicated that while there appears to be a statistically significant multivariate effect between groups effect for Reaction Time, *Post Hoc* pairwise comparisons failed to find a substantial difference between the groups. The data analysed these *post hoc* comparisons using the following equation, taken from Tabachnick and Fidell (2014 P.312) to calculate the revised alpha levels for the univariate results.

EQ1. $\alpha = 1 - (1 - \alpha_1)(1 - \alpha_2)(1 - \alpha_3)$

Where α was the family-wise significance level, α_1 was the alpha level for the first dependent variable, α_2 was the alpha level for the second dependent variable, and α_3 was the alpha level for the third dependent variable.

This formula is different from that used for Bonferroni adjustments in other contexts. For the family-wise α to be $P \leq .05$ or less, the revised α level for each univariate result was $P \leq .015$, which yielded an overall (family-wise) α level of $P \leq .044$. None of the univariate results was significant against the revised univariate α level of $P \leq .015$, although the scores for RTs came close For the RTs, a further adjustment of $\alpha = .015/3$ for the pairwise intergroup comparisons: i.e. $P \leq .005$, however, this failed to yield a significant intergroup comparison

Table 12: *Means and (SD's) for the 2-Back Condition task Performance*

Variable	Controls (CO) *N* = 28	Heavy social drinkers (HSD) *N* = 20	Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22	Significance	*Post-hoc*[1] *1.Control vs HSD* *2.Controls vs HSDCC* *3.HSD vs HSDCC*
Reaction Time	632.386 (171.179)	713.738 (192.326)	597.201 (145.801)	F (2, 66) = 3.617 , P = .032, η_p^2 = .099	1. *n.s* 2. *n.s* *3. n.s*
Correct responses,	10.428 (4.717)	11.050 (3.619)	10.045 (3.344)	F (2, 66) = .323 , P = .725, η_p^2 = .010	1. *n.a* 2. *n.a* *3. n.a*
False alarms	4.428 (4.031)	3.950 (2.762)	3.227 (2.428)	F (2, 66) = 2.345 , P = .104, η_p^2 = .066	1. *n.a* 2. *n.a* *3. n.a*
Misses	3.642 (4.465)	2.850 (3.216)	3.863 (3.121)	Omitted from analysis	1. *n.a* 2. *n.a* *3. n.a*
Correct rejections	27.714 (3.750	28.900 (2.337)	28.863 (1.807)	*H [2, N =70]* =.397 *P*=.820	*1. n.a* *2. n.a* *3. n.a*

1 All Post-Hoc analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .015$

Only three covariates were Normally distributed and offer a full data set; Alcohol consumption in prior six months, No. of hours since last alcohol consumed, and alcohol onset age. Valid stepdown analyses were not possible because of difficulties posed by the measurement of homogeneity of regression in the ANCOVAs with a total of 6 variables to be accommodated (1DV and five covariates). However, multiple linear regression analyses using the covariates as a block of IVs for each DV in the MANOVA model, respectively (i.e. three analyses) showed no significant prediction of the DV.

3-Back Task Performance

Analysis of scores for the 3-Back condition highlighted normal distribution for the raw scores for RTs, % correct responses, and misses without adjustment. There were no outliers for either false alarms or correct rejections. Square root transformations rendered false alarms "normal" but not right sacrifices. Correct rejections were subsequently removed from the MANOVA as both natural log and inverse transformations did not generate correct rejections normal. Nonparametric Kruskal Wallis analysis showed no main intergroup effect for correct rejections. Consideration of correlation scores highlighted that a large correlation led to the omission of misses from the MANOVA.

Scores for homogeneity of variance indicated a significant score for Levene's F for RTs. As with the 2-Back condition, the F_{max} solution rectified this issue (Tabachnick & Fidell, 2014). Variance scores for each of the conditions were as follows: Control group variance = 41,815.4648, HSD variance = 105,501.8739, HSDCC variance = 61,740.0542. The ratio between the smallest and largest variances above is well within this limit. Consequently, the MANOVA results are valid with regards to the homogeneity of variance. The MANAOVA result for inter-group effects was non-significant with Pillai's Trace F (6, 132) = 1.719, *ns*. Data analysis evaluated the univariate results against revised alpha levels calculated using EQ1 above (taken from Tabachnick & Fidell, 2014 P.312). To maintain a family-wise α to be $P \leq .05$ or less, the revised α level for each univariate result was $P \leq .015$, which yielded an overall (family-wise) α level of $P \leq .044$. The univariate result for RTs was marginally nonsignificant. For the RTs, a further adjustment of α = .015/3 for the pairwise intergroup comparisons: i.e. $P \leq .005$. The comparison between controls and binge drinkers was marginally non-significant (P = .006, two-tailed).

MANCOVA solution precluded the inclusion of the covariates; specifically, it would not be possible to complete the step-down analysis with this sample size. However, following Tabachnick and Fidell (2014) using multiple linear regression (MLR) as a means of investigating the relationships between the three covariates as IVs and each DV from the MANOVA. Results indicated that none of the scores for the predictive model (of IVs) was predictive in any of three analyses conducted. However, alcohol consumption in the last six months is worthy of some attention with t (66) = 2.200, P = .031, with a positive B coefficient of 2.553 for the prediction of 3-back RTs. The higher the level of alcohol consumption in the previous six months, the longer the RTs.

Table 13: *Means and (SD's) for the 3-Back Condition task Performance*

Variable	Controls (CO) *N* = 28	Heavy social drinkers (HSD) *N* = 20	Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22	Significance	*Post-hoc*[1] *1.Control vs HSD* *2.Controls vs HSDCC* *3.HSD vs HSDCC*
Reaction Time	610.009 (204.488)	825.487 (324.810)	737.124 (248.475)	F (2, 67) = 4.255, P = .018, η_p^2 = .113	1. *n.a*[2] 2. *n.a* *3. n.a*
Correct responses,	7.000 (4.430)	6.550 (3.872)	5.363 (3.773)	F (2, 67) = 1.023 , P = .356, η_p^2 = .030	1. *n.a* 2. *n.a* *3. n.a*
False alarms	4.428 (4.031)	3.950 (2.762)	3.227 (2.428)	F (2, 67) = .451 , P = .639, ηp^2 = .013	1. *n.a* 2. *n.a* *3. n.a*
Misses	5.776 (4.236)	6.250 (3.338)	7.3636 (3.016)	Omitted From Analysis	1. *n.a* 2. *n.a* *3. n.a*
Correct rejections	28.037 (4.823)	29.050 (2.874)	28.818 (2.383)	*H [2, N =70]* =1.305 *P*=.521	1. *n.a* 2. *n.a* *3. n.a*

[1] All Post-Hoc analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of P ≤ .015

[2] The two-tailed probability for this comparison was $P \leq .006$, which was marginally nonsignificant against the revised alpha level of $P \leq .005$.

Semantic Long Term Memory (COWA)

Analysis of the COWA identified five dependant variables: Letter fluency time (ms), letter fluency total, correct total production (A), Correct production (F), and Correct production (S). Preliminary checks for normality reported abnormal distribution of letter fluency time. The *Z*-scores highlighted four values with scores > ±3.29. The exclusion of these outliers, however, did not render this variable "normally" distributed, so that it was analysed using the Kruskal-Wallis test. Given that the individual letter production scores provide the bases for the calculation of letter fluency totals, and also that the three production scores were highly inter-correlated at r (70) > .87, the researchers decided not to analyse these individual variables. Letter fluency total was normally distributed and was analysed using univariate ANOVA. This analysis did not show an inter-group effect (F < 1). While *Post hoc* pairwise comparisons indicated, that letter fluency time and letter fluency total were not significantly correlated with each other and so were both examined concerning effects with the covariates, letter fluency did not correlate with any additional covariate. Table 14 summarises the results for the COWA.

Table 14: *Means and (SDs) for Semantic Long Term Memory (COWA) task Performance*

Variable	Controls (CO) *N* = 28	Heavy social drinkers (HSD) *N* = 20	Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22	Significance	*Post-hoc*[1] *1.Control vs HSD* *2.Controls vs HSDCC* *3.HSD vs HSDCC*
Letter fluency time (ms),	524076.178 (679875.016)	81795.500 (784885.0643)	707688.727 (992221.253)	*H* [2, N =70] =.981 *P*=.612	1. *n.a* 2. *n.a* *3. n.a*
Letter fluency, Correct total production	61.428 (23.864)	54.650 (26.672)	62.409 (25.104)	*F*(2,67) = .600, *P* = .552, ηp^2 = .018	1. *n.a* 2. *n.a* *3. n.a*
(A), Correct production	17.535 (8.319)	15.150 (7.328)	18.272 (7.808)	Omitted from Analysis	1. *n.a* 2. *n.a* *3. n.a*
(F), Correct production	18.785 (9.398)	18.000 (10.120)	21.454 (10.931)	Omitted from Analysis	1. *n.a* 2. *n.a* *3. n.a*
(S). Correct Production	25.785 (9.818)	20.300 (11.145)	25.909 (11.501)	Omitted from Analysis	1. *n.a* 2. *n.a* *3. n.a*

1 All Post-Hoc analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .015$

Wisconsin Card Sorting Test Task Performance

Analysis of the WCST generated three potential DVs: completion time (ms), totally correct and error rate. Normality scores indicated the only normal distribution was for error rate in its raw score form. Frequency *Z*-scores for the two remaining DV's stated that there were no outliers at the cut off of ± 3.29 for Completion Time while analysis of the scores for Total Correct highlighted two, this then rendered the DV normally distributed ($N = 68$). Subsequent square root transformations resolved the issue of normality for completion time. For the variables chosen for MANOVA ($N = 68$), there were no significant inter-correlations between square root transformations of completion time, totally correct, and error rate. MANOVA did not show a significant main effect between groups with Pillai's trace F (6, 128) = 1.562, *ns.* Analysis of Box's *M* statistic reported a highly substantial score with analysis of the variances between cells suggestive of a violation of the test assumptions. Total correct and transformed completion time scores were unsuitable for analysis as Levenes. *F* identified issues with homogeneity of variance. Thus MANOVA was rendered unfit for this analysis.

The problems identified with MANOVA did not, however, automatically invalidate the subsequent use of MANCOVA. However, when the covariates of alcohol consumption in the prior six months, the number of hours since last alcohol consumed, results included alcohol onset age and cannabis consumption in the previous six months. There was again a highly significant value for Box's *M* statistic, combined with a tendency for higher variances in the smallest group (i.e. Binge Drinkers). Consequently, the data will not report the MANCOVA results here due to the violations of the assumption of homogeneity of variance and covariance matrices.

Total correct and error rates scores were analyses using a Univariate ANOVA, and Kruskal Wallis test, with a Bonferroni, adjusted alpha level of $P \leq .025$ for main effects and $P \leq .008$ for inter-group comparisons. Results failed to show a between-groups difference for either Total Correct ($F < 1.$) or Error Rate ($F < 1.$), nor did the nonparametric ANOVA for Completion Time. *Post-Hoc* pairwise comparisons reported no significant correlations. Table 15 summarises the results for the WCST.

Table 15: *Means and (SDs) for The Wisconsin Card Sorting Task Performance*

Variable	**Controls (CO) *N* = 28**	**Heavy social drinkers (HSD) *N* = 20**	**Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22**	**Significance**	***Post-hoc*[1] *1.Control vs HSD 2.Controls vs HSDCC 3.HSD vs HSDCC***
Completion Time (ms),	323582.357 (120835.896)	296594.500 (93636.772)	383382.045 (164115.728)	*H* [2, *N* = 70] = 2.997 *P* = .223	1. *n.a* 2. *n.a* *3. n.a*
Total Correct	79.821 (9.193)	73.650 (17.806)	73.909 (15.931)	*F*(2,67) = .801, *P* = .453, ηp^2 = .024	1. *n.a* 2. *n.a* *3. n.a*
Error Rate	44.178 (16.688)	51.050 (21.192)	47.454 (21.000)	*F* (2,67) = 0.732, *P* = .485, ηp2 = .021.	1. *n.a* 2. *n.a* *3. n.a*

1 All Post-Hoc analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .015$

Computerised Visuospatial Grid Task

Analysis of the Grid Task highlighted four dependent variables: completion time, totally correct, memory span, and memory total. Scores for total correct and memory span revealed that result highlighting the "normal" distribution of these scores, but completion time and memory total were not. Following this, frequency *Z*-score analysis indicated that there were no outliers for memory total or for completion time. Normalisation calculations for memory total were effective via square root transformations with an N =70. The square root transformations of total scores correlated too highly with the total correct for the analysis (r (70) = .908, $P \leq$ .000, two-tailed). The correlations for the three remaining variables were acceptable. With significant correlations identified for memory span and correct total (r (70) = .639, $P \leq .000$, two-tailed), and $\log_n$ transformations of completion times and correct total (r (70) = .350, $P \leq$ *.001*, two-tailed). Correlations between memory span and Log_n transformations for completion time were non-significant (r (70) = .226, P = .060). The resulting MANOVA did show a borderline non-significant result (Pillai's trace F (6, 132) = 2.049, P = .064), with no significant inter-group comparisons. However, Box's M was highly significant (P < .000), and the step-down analysis failed to show homogeneity of regression for memory span and for the ln completion times so that the validity of the MANOVA result is questionable.

The MANCOVA solution included four covariates from the six previously identified; precisely, Alcohol consumption in the prior six months, number of hours since last alcohol consumed, alcohol onset age, cannabis consumption in the previous six months. However, the amount of cannabis used in the last six months was not normally distributed and removed from the analysis. However, Homogeneity of regression was not achieved for alcohol onset age, so that the investigation did not pursue the MANCOVA further.

In light of the problems with the multivariate results, the dependent variables total correct, and results analysed memory span, which met the conditions for ANOVA in that way. At the same time, the completion time was suitable for Kruskal Wallis analysis. The revised Bonferroni alpha level for main effects was $P \leq .017$, and inter-group comparisons used an adjusted alpha level of $P \leq .006$ two-tailed. Table 16 summarises the results for the VSWM task

Table 16: *Means and* (*SD's*) for the Computerised Visuospatial Grid Task.

Variable	**Controls (CO) *N* = 28**	**Heavy social drinkers (HSD) *N* = 20**	**Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22**	**Significance**	***Post-hoc*[1] *1.Control vs HSD 2.Controls vs HSDCC 3.HSD vs HSDCC***
Memory Span	5.642 (1.591)	5.250 (.910)	5.272 (1.351)	$F < 1$	1. n.a 2. n.a 3. n.a
Completion Time, Total	197640.321 (57737.0199)	223893.200 (90398.257)	207968.681 (88201.237)	H [2, N = 70] = 1.335,P =.513.	1. n.a 2. n.a 3. n.a
Correct Total	7.964 (2.411)	7.500 (2.564)	8.954 (2.853)	F (2, 67)= 1.749, P =.182,ηp^2=.050	1. n.a 2. n.a 3. n.a
Memory Total	7.964 (2.411)	7.500 (2.564)	2.564 (2.564)	Omitted from analysis	1. n.a 2. n.a 3. n.a

[1] All *Post-Hoc* analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .01$

Univariate ANCOVAs using reports of alcohol units consumed in the previous six months, number of hours since last consumption of alcohol, and alcohol onset age were conducted, with their results evaluated against the same revised alpha levels as for the ANOVAs. There was a significant intergroup effect for memory span (F (2, 64) = 6.889, P = .002, η_p^2 = .177), with only the *post hoc* inter-group comparison being that between the controls and the HSDCC group, with the control group having a significantly longer span (P < .000 two-tailed). Data analysis performed a multiple linear regression to examine the relationships between group membership (transformed into a dummy variable) and the covariates identified in Chapter 5 serving as independent variables (IVs), and VSWM span as the DV. Table 17 shows the order of hierarchical entry of IVs into the regression solution.

Table 17: Sequence of IV inclusion for the Regression Model

Model	IV
1	HSD V Others,
	HSDCC V Others
2	HSD V Others,
	HSDCC V Others
	Hours since last Alcoholic Drink
3	HSD V Others,
	HSDCC V Others
	Hours since last Alcoholic Drink
	Alcohol consumed in the last six months (units)
4	HSD V Others,
	HSDCC V Others
	Hours since last Alcoholic Drink
	Alcohol consumed in the last six months (units)
	Age of first alcohol use (years)

The results indicated that correct pattern recognition with the transformed group variables entered alone in model 1 was non-significant. Tables 18 and 19 reports on the hierarchical multiple linear regression scores, the regression solution did present significant results at model 2, where hours since the last alcoholic drink was added to the model and contributed to 11.4% of the score. The inclusion of Alcoholic units consumed in the past six months also proved to be significant in model 3, contributing to 18.9% of the total variance in span scores. The statistics for model 4 were also substantial, where results showed that the inclusion of age at

first use of alcohol accounted for 35.1% of the total variance in span scores. Significant F_{change} values for Models 2, 3, and 4, indicating that each new covariate added significantly improved prediction for memory span scores.

Table 18: Summary of regression analysis for VSWM span scores

Model	R^2	R^2 change	*F* change	df1	df2	*Sig F* change
1	.020	.020	.668	2	67	*n.s*
2	.114	.094	7.204	2	66	*P* ≤.010.
3	.189	.075	6.054	2	65	*P* ≤.017.
4	.351	.162	*15.952*	1	64	*P* ≤.000.

Table 19: ANOVA for VSWM span scores

Model	Component of variance	df	MS	*F*	Sig.
1	Regression	2	1.222	.668	.516
	Residual	67	1.830	-	-
	Total	69	-	-	-
2	Regression	3	4.734	2.827	.045
	Residual	66	1.679	-	-
	Total	69	-	-	-
3	Regression	4	5.918	3.797	.008
	Residual	65	1.559		
	Total	69	-	-	-
4	Regression	5	8.777	6.925	.000
	Residual	64	1.268	-	-
	Total	69	-	-	-

Concerning the individual predictors in model 4, the combining of two groups in each of the dummy variables renders unclear the interpretation of the *t*-test results for the HSD versus others IV (t (65) = 2.222, P = .030) and the HSDCC versus other IV (t (65) = 3.707, P < .000). Both of these IVs showed positive *B* coefficients of 0.927 and 1.520, respectively. However, the result for the HSDCC versus other IV does show that scores significantly associated higher VSWM span with not having used cannabis. With regards to the covariates, alcohol units consumed in the previous six months showed a significant effect (t (65) = 2.239, P = .029), with the positive *B* coefficient of 0.012 had a positive relationship with VSWM span. The onset age for alcohol use also had a significant relationship with VSWM span (t (65) = -3.994, P < .000) with the negative *B* coefficient of -0.092 showing younger-onset ages to be associated with better VSWM span scores.1

Discussion

With regards to measures of IR, the number series task scores indicated that the only performance measure to show a significant difference between the groups was the number of correctly recognised patterns. Results indicated a significantly higher total for correct recognition for the CO group compared to the HSD group, with no other inter-group comparisons being significant. This pattern of scores is entirely consistent with findings from within the academic literature, serving to highlight the neurotoxic effects of HSD on IR task performance (Briere et al. (2019). Crean et al. (2012) noted that there was a lack of studies looking at the relationship between cannabis use and IR. The present results did not find any significant inter-group comparisons or correlations with covariates identified in chapter 5 limits to support an assertion that cannabis use contributes to impairments in this area of EF functioning. However, further research is a need in this area, with the potential role discussed further below of a neuroprotective effect related to cannabis consumption being part of such research (Thayer et al. 2019; Toriño et al., 2010; Rubio et al., 2011)

Results for VSWM task performance demonstrated that the control group showed significantly higher visuospatial memory span scores compared to the HSDCC group following the introduction of the covariates. This pattern of results is consistent with findings within the academic literature related to THC induced impairment to VSWM (Skau et al., 2019), and with the findings of Wareing et al. (2004). They reported that cannabis use was a significant covariate of VSWM performance in comparisons of ecstasy users to drug naïve controls. However, the results from the regression analysis pose a problem in that alcohol consumption in the previous six months showed a positive relationship to VSWM span, while onset age for drinking showed a negative relationship to VSWM span. In other words, higher levels of recent usage and younger onset were both related to higher span scores. These scores are contrary to other findings concerning VSWM performance in substance users (Barnes et al., 2018), and suggests that further research into the relationship between alcohol consumption and VSWM performance is necessary. The evidence for a relationship cited here between cannabis consumption and VSWM performance highlights the need for poly-substance use accounted for in the further investigation of effects related to alcohol.

Concerning the remaining cognitive functions, HSDCC participants showed faster RTs for 'GO' responses in the GO/No-GO task of inhibitory control (IC) than both other groups. However, there were no significant differences in other measures of performance, such as those concerning errors and correct responses, to suggest whether scores relate this difference to better or worse task performance overall. However, result interpretation may see these result for RTs as consistent with the generally higher scores for impulsivity reported for HSDCC participants in Chapter 5. One further explanation for this pattern is the potential neuroprotective effects of cannabinoids. CBD acts against the neurotoxic effects of HSD and THC (Toriño et al., 2010; Rubio et al., 2011). To date, there does not appear to have been any study of potential neuroprotective effects of cannabis use in the context of human alcohol consumption, and it is essential to emphasise that the present study does not test such a hypothesis. Nevertheless, the possibility of such an effect being present in the data obtained from the participant groups studied is one which should be acknowledged.

Concerning the other cognitive functions examined, the present data set fails to show any statistically significant differences between the HSDCC, HSD, and CO groups with regards to access to semantic long-term memory and ESS task performance. It is important to note that interpretation should see these results in the context of inconsistent findings regarding these functions (Blaes et al., 2019) and that further research will inevitably be necessary for a clearer picture to emerge.

It is worth noting also that the scores for the N-Back task conditions fail to find any statistically significant effects for the 0 and 1 back conditions. These results were in keeping with products from the academic literature. Indeed research by Morgan et al. (2016) and Vandrey et al. (2013) have noted that the 0-Back and 1-Back are not sufficiently demanding to highlight any cognitive impairment in HSD and cannabis smoking populations. At the same time, there was a statistically significant multivariate main effect for RTs in the 2-Back condition. The lack of substantial univariate effects and *post-hoc* comparisons, together with there being no meaningful relationships between the covariates studied and task performance, limits any conclusions. However, the results for the 3-back condition showed that impaired performance presented itself through a marginally nonsignificant difference concerning slower RTs for the HSD group compared to the CO group. A subsequent multiple linear regression analysis

showed a significant positive relationship between RTs and alcohol consumption in the previous six months. Chapter 5 reported that this measure of alcohol consumption was significantly higher for the HSD group than the CO group, which is consistent with the RT difference between the groups. Chapter 5 also showed the HSDCC group to have significantly higher alcohol consumption in the previous six months than the control group. The HSD and HSDCC groups are not significantly different on this measure of alcohol consumption, which would seem to be inconsistent with the lack of any difference between the HSDCC and CO groups on task performance. It is clear, therefore, that further investigation into the respective relationships of alcohol and cannabis to account at the 3-back level of this task is required. It was also highlighted by Hopestaken et al. (2015), that there tends to be a drop off in task performance on all condition post-2-Back as all following conditions elicit a degree of cognitive overload. Consequently, the present results from the 3-Back may reflect the influence of other factors on task performance which are not necessarily a consequence of substance misuse. In this regard, Chapter 5 reported that the HSDCC group scores more highly than both other groups on premorbid IQ and, of more relevance to the 3-Back results, more highly on fluid intelligence (i.e. Raven's Matrices) than the HSD group.

The varied nature of these results may reflect the indeterminate nature of scores within the current literature (Briere et al., 2019; Calabria et al., 2019; Schult et al., 2019;). A potential explanation for this observed patterning is that this is reflective of the relative robustness of specific EF and WM domains with regards to HSD and HSDCC induced damage (Robinson et al., 2009). Indeed neurocognitive research argues that WM and EF have a diffuse network of the neural substrates supporting both WM and EF task performances. These include cortical (DLPFC) and sub-cortical structures such as the Thalamus (Tomasi & Chang, 2005; Ullman et al., 2014, Zimmer, 2008) therefore HSD and HSDCC induced reductions in cortical functionality would not necessarily equate to noticeable decreases in EF task. Fisk and Montgomery (2011) note that these inconsistencies are associated with task insensitivity to subtle alterations in task performance observed in younger HSD and cannabis smoking populations. Montgomery and Fisk (2008) argue that the introduction of supplementary imaging technology could address this issue. In this way, research would benefit from complementary neuroimaging or neurophysiological data to elucidate on the findings of the cognitive functions tests.

A limitation of this study is about the failure to report upon nicotine consumption levels as introduced in chapter 5. Nicotine affects cognitive task scores. Evans et al., (2009) reported that nicotine exerts a neurotoxic effect upon the DLPFC, which in turn reduces functionality with regards to both WM and EF. In the study, the author reported that cannabis smokers performed worse on all measures of WM and EF compared to controls. It is, therefore, entirely plausible that nicotine could be affecting the scores reported in this study. However, the failure to report upon the levels of nicotine consumption renders it impossible to explore its potential impact here

In conclusion, the present results appear to suggest that the HSDCC participants showed effects on their cognitive functionality within the domains of IC and VSWM. At the same time, there also exists the potential for the neuroprotective properties of CBD exerting itself upon IC task performance. There was evidence for HSD participants showing effects on their IR and EU functioning, although the role of alcohol in these effects was unclear due to the lack of impact demonstrated by the HSDCC group. Despite the inconsistent nature of scores, these findings represent an advance in our knowledge of EF and WM performance in HSD and HSDCC participants, in addition to highlighting a need for further research. Supplementary neuroimaging data can highlight possible activity in a wide range of neural substrates to counter the potential insensitivity of current WM and EF tasks.

Chapter 8.

HSD and cannabis use: implications for Oxy and De-Oxy Hb concentrations during EF and WM tasks

Introduction

Marinkovich et al. (2011) attributed the results from EF and WM research in both HSD and cannabis consumption to issues in neuropsychological assessment sensitivity. The authors suggested that research could address the issues surrounding the detection of subtle alterations in task performance constructively through the introduction of supplementary imaging technology. Research would benefit from complementary neuroimaging and neurophysiological data to elucidate on the findings of the cognitive functions tests. Studies conducted by Roberts and Montgomery (2015) noted that functional near-infrared spectroscopy (fNIRS) is a reliable measure of regional cerebral blood flow (rCBF) for the assessment of cognitive effort during task performance. In particular, increases in Oxy-Hb and Deoxy-Hb is indicative of increased resource allocation to meet task demands. Specifically, an increase in the volume of oxygenated blood flow entering a region of interest (ROI), or the increased utilisation of Oxy-Hb, which leads to a subsequent rise in Deoxy-Hb concentrations would show such a change.

Conversely, decreases in Oxy-Hb and Deoxy-Hb concentrations are indications of decreased cognitive engagement. Cerebral blood flow volumes fall in a given ROI as participants struggle to engage with a cognitive task or when they actively disengage with a job owing to an overload of task demands. Studies concerned with polydrug use and inhibitory control (IC) mainly focus on ecstasy consumption.

Roberts and Montgomery (2015) reported the combined use of an IC task with fNIRS with users of ecstasy. The results showed no difference between the users and non-using controls on task performance reporting differences between the two groups on rCBF during task performance regarding changes from baseline. In particular, results reported changes in Oxy-Hb levels in the right prefrontal cortex (PFC) and dorsolateral prefrontal cortex (DLPFC) between the groups. Although studies did not use *f*NIRS with either HSD or Cannabis

consumption research, the researchers used Go/No Go task, for this present study (see Chapter 6) was used alongside other neuroimaging and neurophysiological measures. The findings of which provided a more in-depth insight into the relationship between brain activity and IC performance in participants characterised by HSD and cannabis consumption. For example, Lopez-Caneda et al. (2014) used the Go /No Go task to examine neural activation patterns in the PFC during IC performance in HSD participants. Event-related potentials (ERPs) track the changes in activation patterns over several years, thus providing insight into the aetiological progress neurological alterations occurring within HSD participants. Results indicated that the study significantly correlated reduced amplitude in activity with an earlier age of onset of alcohol consumption than the period stipulated in the DSM V criteria for HSD, as well as with greater quantity and speed of alcohol consumption. Regression analysis showed that amplitude alterations during response inhibition in the No-Go condition were a significant predictor of the rate of alcohol intake and the age of onset of regular drinking. Intergroup comparisons demonstrated that engaging in HSD for a minimum of 2 years, resulted in significantly larger NoGo-P3 amplitudes than controls. These findings suggest that not only do HSD participants display more significant impairment to IC task performance than non-HSD participants but also that an early onset of HSD may impair the neural functioning related to inhibitory processes.

The Go /No Go task has also been used in conjunction with imaging technology to provide deeper insights into the effects of cannabis consumption on IC. In a study conducted by Hester and Garavan (2009), the researchers used the Go/No-Go task to conjunction with fMRI. Results indicated that the cannabis smoking group performed worse than controls, with a more significant number of errors recorded as well as a considerable deficit in awareness of commission errors. Results also indicated that cannabis users showed reduced behavioural monitoring capacity associated with hypoactivity DLPFC. The observed increase in the occurrence of hypoactivity was statistically significant when correlated with error-awareness rates. These findings not only confirm the observations that cannabis consumption is associated with reduced IC functioning. But also that the results may highlight the difficulties in cognitive control and the monitoring of interoceptive awareness in chronic drug users as a potential behavioural trait that would contribute to the maintenance of cannabis abuse.

As with IC, neuroimaging tools have been successfully implemented in studies investigating inductive reasoning (IR). Meintjes et al. (2019) were able to combine IR assessments with fMRI data. The authors compared HSD young adults (N = 15) to controls (N = 18) with regards to IR task performance using a number series task where the analysis required participants to recognise the pattern in a numerical sequence and select from options, the next number in the series. While results recorded no significant difference between the groups with regards to behavioural task performance, fMRI analysis indicated that the HSD group engaged in more effortful cognition to maintain baseline scores. Results explicitly demonstrated that the HSD group required the recruitment of additional cortical networks, specifically the left and right angular gyrus and posterior cingulate cortex and precuneus. During tasks that required more in-depth analyses such as the addition of number strings, the HSD group also displayed more diffuse and widespread activation of other networks, including the cerebellar vermis.

IR research also used *f*MRI concerning the effects of cannabis consumption on this aspect of functioning. Moeller et al. (2010) reported that while cannabis users did not display any behavioural deficits with regards to IR using the Number Series Task, *f*MRI recordings showed significant differences in the HSD group comparative to drug naïve controls. Expressly, results indicated that the HSD group reported increase activation of cortical networks in the DLPFC compared with non-drug-using controls, during task performance. In another study, Campanella et al. (2013) reported results comparing the task performances of (N = 16) cannabis smokers and (N = 16) non-smoking controls on a 2-Back condition from a traditional N-Back paradigm. While the cannabis smokers performance did not significantly differ from the control group, the fMRI analysis indicated that cannabis smokers displayed an increase in PFC activity, with an increase in bilateral activation of the pre-supplementary motor area. Analysis of behavioural data reported a positive correlation between the estimates of joints consumed per episode and activation levels of the dorsomedial prefrontal cortex and increases in the cerebellum, thalamus, and insula. Thus the authors concluded that cannabis smoking could lead to compensatory actions within the brain that enable smokers to facilitate executive updating perforce relative to controls, at the cost of neurological activity.

In contrast to the literature on IC and IR functioning, there appears to be a lack of studies using the N-Back paradigm with substance-using populations which have used fNIRS to provide measures of task-related rCBF changes. Concerning *f*MRI data, Pferbaum et al. (2001) examined the effects of HSD on executive updating with participants completing a 2-back Paradigm. Whilst the results of this study indicated that there appeared to be no significant difference between the two groups on relative task performance. Analysis of *f*MRI data suggested that the HSD reported greater activation of the PFC, specifically Brodmann's area's 9, 10 and 45, regions implicated in the processing of executive updating. Therefore Crews et al. (2000) has suggested that consideration of cortical activation patterns is a requirement of HSD research. These findings offer more in-depth insight and clarity around any potential neurocognitive effects and the compensatory actions of cortical structures. Montgomery et al. (2012) conducted a meta-analysis on EF task performance in HSD populations. Results indicated that the trends within the academic literature are suggestive of no significant difference with regards to behavioural task performance in EU when assessed using the N-Back paradigm, consistent with the findings of Pferbaum et al., (2001). Concerning cannabis use, Fisk and Montgomery (2008) failed to find a significant between-group difference with regards to EU performance on the N-Back test in cannabis-using participants. Given the potential contributions of both alcohol and cannabis to impaired cognitive functioning reviewed in chapters 1 to 4 of this thesis. It appears that there is a need for research into the respective HSD and cannabis consumption n EU functioning, which incorporates task-related changes in brain functioning alongside task performance data.

Fisk and Montgomery (2016) propose that data on brain structure and functioning could provide insights concerning the inconsistent results reported for Access tasks, in addition to issues of test insensitivity. Again, the introduction of supplementary imaging technology could address this. Chanraud et al. (2009) reported that CWFT performance decreased in an HSD population ($N = 31$), compared to drug naïve control (N = 28). Analysis associated these scores with decreases in grey matter concentrations in the left and right dorsolateral frontal cortex (up to 20% lower). The study saw this reduction to a lesser extent in the temporal cortex, insula, thalamus, and cerebellum. Decreases in white matter volume were widespread, being up to 10% in the corpus callosum. Data analysis correlated reductions in CWFT with grey matter volume decreases in the frontal lobe, insula, hippocampus, thalami and cerebellum, and with white matter decrease in the brainstem.

Additionally, Churchwell et al. (2010) reported cannabis users (*N* = 18) displayed no behavioural deficits compared to drug naïve controls (*N*= 17) with regards to Access task performances through the use of CWFT. The fMRI analysis did demonstrate significant morphological differences between cannabis using and drug naïve controls. Specifically, cannabis smokers reported decreased volume in the Right PFC.

A similar pattern of apparent test insensitivity to performance differences between substance users and nonusers was also reported by Zehra et al. (2019) for executive set-shifting (ESS) performance using the Wisconsin Card Sorting Task (WCST). In this study, HSD participants (*N*=19) compared to drug naïve controls (*N* =23), with no differences reported for WCST performance. However, *f*MRI analysis indicted that the HSD group recorded higher activation patterns in neurological structures associated with ESS, specifically parietal and prefrontal cortices and the occipital cortex. Research has also applied imaging technology to the WCST performance of cannabis users. Imaging technology has also been used to significant effect elucidate the impact of HSD on visuospatial working memory (VSWM) task performance. For example, Squeglia et al. (2011) compared 40 HSD's to 50 non-drinking controls. Their *f*MRI results indicated that HSD participants engaged in more effortful cognition to maintain VSWM task performance than the controls. Specifically result shown that the HSD group reported greater bilateral activation of frontal, anterior cingulate, temporal, and cerebellar cortices compared to controls. Studies also researched the use of *f*NIRS in ecstasy/cannabis polydrug use task performance. Montgomery and Fisk (2017) compared (*N* = 20) cannabis/ecstasy, polydrug users, too (*N* = 20) drug-naive controls with results indicating that there was no significant difference between the groups concerning VSWM updating performance. However, the polydrug users did show a significant between-group difference for VSWM task difficulty. Analysis of haemodynamic responses indicated that substantial increases in Oxy-Hb and Deoxy-Hb are suggestive of the Polydrug users engaging in more effortful cognition to meet task demands.

The present study gathered data on regional cerebral blood flow (rCBF) using fNIRS from participants as they completed the tasks reported in Chapter 7 of this thesis. Results predicted that results would associate changes from baseline in rCBF during task performance with previous exposure to alcohol and cannabis intake.

Methods

Design

Chapter 5 details the research design in Design sub-section. The task performance-dependent variables (DV) are the changes from baseline in Oxy-Hb and Deoxy-Hb blood.

Participants

Chapter 5 details the participant recruitment, inclusion and exclusion criteria in the design sub-section.

*f*NIRS Data Collection Procedure

Measures of the changes in rCBF accompanying task performance used a continuous-wave OxyMon *f*NIRS system developed by Artinis Medical Systems (Elst, The Netherlands). Table 20 details the regions of interest (ROIs). Taking recordings from these ROIs involved the placement of optodes over areas of the left and right dorsolateral/medial prefrontal cortex. These corresponded to locations F3. F4. F7 and F8 of the 10-20 system). The researcher fitted the optodes within a standard EEG cap to allow the precise locations for recording. Table 20 also shows the corresponding Brodmann areas for these ROIs.

Details of the recruitment, screening, and the group allocation process are in the Procedure sub-section of chapter 5. The researcher debriefed the participants about data collection using *f*NIRS, including the placing of the optodes on their head. The researcher then fitted an EEG cap containing the optodes appropriately on their heads, and the baseline readings are taken whilst watching the nature video. The administration of cognitive tasks then followed this. Upon completion of the tests of cognitive function, the researcher then removed the EEG cap, and the researcher then debriefed the participants.

Table 20: Optode placement used in the 10-20 system and corresponding Brodmann areas procedure

ROI[1]	10-20 system position	Brodmann area
Right inferior PFC	AF8	10
Right superior PFC	AF4	9
Right inferior DLPFC	F6	46
Right superior DLPFC	F4	8
Left inferior PFC	AF7	10
Left superior PFC	AF3	9
Left inferior DLPFC	F5	46
Left superior DLPFC	F3	8

1 Prefrontal cortex (PFC): dorsolateral prefrontal cortex (DLPFC)

Analytic Strategy

The rCBF data were analysed for each task in two halves, corresponding to data from the left and right hemispheres, respectively. In addition to limiting the number of DVs in each multivariate analysis, this distinction also took into account differences in functioning between the two cerebral hemispheres. Data on the changes from baseline for Oxy-Hb and Deoxy-Hb were examined for deviations from a normal distribution concerning *z*-scores for skewness and kurtosis, as described by Tabachnick and Fidell (2014). Consequently, decisions regarding the use of either parametric MANOVA, MANCOVA or a nonparametric Kruskal-Wallis analysis for inter-group comparisons for Oxy Hb and De-oxy Hb for each ROI, were made in the light of the distribution of the data. Following the guidance of Tabachnick and Fidell, data analysis also used multivariate linear regression (MLR) to examine the relationship of covariates to the rCBF in cases where scores did not meet the assumptions of MANCOVA. Data analysis evaluated univariate results against adjusted alpha levels calculated using EQ1 reported in Chapter 6, taken from Tabachnick and Fidell (2014 P312).

The study conducted pairwise *post hoc* analyses where results showed a significant main effect across participant groups. These comparisons were two-tailed against a Bonferroni adjusted alpha level, calculated using the univariate alpha level as the numerator in this calculation, and three as the denominator, representing the three participant groups. In the case of variables differing significantly from a normal distribution, analysis employed the Mann-Whitney *U* test

for the *post hoc* intergroup comparisons. As the study recorded levels of Oxy-HB and Deoxy-Hb deviations from baseline, a verification procedure was used by which a version of these variables added a constant to render all values as positive. Although the analysis did not use these transformed variables in the final analysis, they did serve to confirm the interpretation of the data reported below.

Results

*f*NIRS response to the Go/No-Go Task

The nature of the fNIRSs resulted in the study producing the same 8 DV's for analysis of both left and right hemispheres across all of the EF and WM measures. Specifically, the 8 DVs were: Oxy inferior PFC, Deoxy inferior PFC, Oxy superior PFC, Deoxy superior PFC, Oxy inferior DLPFC, Deoxy inferior DLPFC, Oxy superior DLPFC, and Deoxy superior DLPFC.

Right hemisphere. Preliminary analysis of skewness and kurtosis scores for the Go/No-Go task identified that Oxy-Hb inferior PFC, Oxy-Hb superior PFC, Deoxy-Hb superior PFC, and Oxy-Hb superior DLPFC, were all normally distributed. The Z-Score analysis identified scores which violated *z*-Score limits of $z = \pm 3.29$, for Deoxy-Hb inferior PFC, Oxy-Hb inferior DLPFC, Deoxy-Hb inferior DLPFC, and Deoxy-Hb superior DLPFC. The removal of one participant rendered all variables normally distributed save for Oxy-Hb inferior DLPFC. The analysis omitted scores for Deoxy-Hb inferior PFC from MANOVA because of a high positive correlation with Oxy-Hb inferior PFC. Multivariate and univariate analysis did not find a significant effect between groups (Pillai's Trace $F < 1$). None of the nonparametric comparisons was substantial either. Table 21 shows the rCBF results for the right hemisphere on this task.

Table 21: *f*NIRS Right Hemisphere Oxy and Deoxy-Hb changes from baseline for the Go/No-Go Task

Variable	**Controls (CO) *N*= 28**	**Heavy social drinkers (HSD) *N* = 20**	**Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22**	**Significance**	***Post-hoc*[1] *1.Control vs HSD 2.Controls vs HSDCC 3.HSD vs HSDCC***
Oxy-Hb Right Inferior PFC	.194 (3.963)	.101 (3.560)	1.108 (3.599)	*F* (2, 64) =5.159, *P*=.409,ηp^2= .666	*1. n.a 2. n.a 3. n.a*
Deoxy Right Inferior PFC	-.957 (2.019)	-.847 (2.030)	-.163 (1.557)	*H* [2, *N* = 70] = 3.686 *P* = .186	*1. n.a 2. n.a 3. n.a*
Oxy Right Superior PFC	-.273 (3.331)	-.159 (2.401)	-1.009 (3.303)	*F* (2, 64) =3.344, *P*=.385,ηp^2= .683	*1. n.a 2. n.a 3. n.a*
Deoxy Right Superior PFC	-.906 (1.817)	-.748 (1.686)	-1.067 (1.821)	*F* (2, 64) =.194, *P*=.063,ηp^2= .939	*1. n.a 2. n.a 3. n.a*
Oxy Right Inferior DLPFC	.945 (3.426)	1.211 (5.346)	-.284 (3.097)	*H* [2, *N* = 70] =1.125 *P* = .977	*1. n.a 2. n.a 3. n.a*
Deoxy Right Inferior DLPFC	-.798 (2.102)	-.471 (3.682)	-1.305 (1.434)	*H* [2, *N* = 70] = .047 *P* = .	*1. n.a 2. n.a 3. n.a*
Oxy Right Superior DLPFC	.270 (3.018)	1.605 (2.785)	.319 (3.557)	*F* (2, 64) =5.473, *P*=.611,ηp^2= .546	*1. n.a 2. n.a 3. n.a*

Deoxy	Right	-.343	.592	-.195	*H* [2, *N* = 70] =	*1. n.a*
Superior		(1.558)	(2.565)	(1.420)	1.429 *P* = ..490	*2. n.a*
DLPFC						*3. n.a*

[1] All *Post-Hoc* analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .01$

Left hemisphere. Analysis of Oxy-Hb and Deoxy Hb changes in the left hemisphere identified the normal distribution of scores Oxy-Hb inferior PFC, Oxy-Hb inferior DLPFC, and Oxy-Hb superior DLPFC. The *z*-score analyses identified outliers for Deoxy-Hb inferior PFC, Oxy-Hb superior DLPFC, Deoxy-Hb superior DLPFC, and Deoxy-Hb superior PFC. Removal of these scores failed to normalise the results as did subsequent transformation procedures. Multivariate analysis was unable to find a statistically significant intergroup with Pillai's Trace ($F < 1$).

Furthermore, there were no significant univariate effects or intergroup comparisons. Nor did any of the nonparametric tests identify a substantial impact for any region of interest. Table 22 shows the rCBF results for the left hemisphere on this task.

Table 22: *fNIRS* Left Hemisphere Oxy and Deoxy-Hb changes from baseline for the Number Series Task

Variable	Controls (CO) *N* = 28	Heavy social drinkers (HSD) *N*= 20	Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22	Significance	*Post-hoc*[1] *1.Control vs HSD 2.Controls vs HSDCC 3.HSD vs HSDCC*
Oxy-Hb Left Inferior PFC	-.234 (2.823)	-.553 (3.169)	.221 (3.282)	*F* (2, 64) =.012, *P*=.988,ηp^2= .000	*1. n.a 2. n.a 3. n.a*
Deoxy Left Inferior PFC	-.533 (2.357)	-.174 (3.106)	-.586 (1.926)	*H* [2, *N* = 70] = 311 *P* = .856	*1. n.a 2. n.a 3. n.a*
Oxy Left Superior PFC	-.419 (3.876)	-.830 (5.606)	-.306 (3.857)	*H* [2, *N* = 70] = .633 *P* = .793	*1. n.a 2. n.a 3. n.a*
Deoxy Left Superior PFC	-.562 (6.928)	-2.699 (10.047)	-1.442 (7.138)	*H* [2, *N* = 70] = .117 *P* = ..943	*1. n.a 2. n.a 3. n.a*
Oxy Left Inferior DLPFC	-1.905 (5.105)	-2.735 (6.573)	-1.682 (5.562)	*H* [2, *N* = 70] = 1.142 *P* = .565	*1. n.a 2. n.a 3. n.a*
Deoxy Left Inferior DLPFC	-1.792 (3.232)	-2.630 (4.784)	-1.829 (3.641)	*F* (2, 64) =.253, *P*=.777,ηp^2= .008	*1. n.a 2. n.a 3. n.a*
Oxy Left Superior DLPFC	-.656 (5.603)	-1.494 (5.562)	-.989 (5.889)	*F* (2, 64) =.104, *P*=.901,ηp^2= .003	*1. n.a 2. n.a 3. n.a*

Deoxy	Left	-1.224	-1.162	-1.627	*H* [2, *N* = 70] =	*1. n.a*
Superior		(5.787)	(5.221)	(6.296)	.187 *P* = .911	*2. n.a*
DLPFC						*3. n.a*

[1] All *Post-Hoc* analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .01$

*f*NIRS response to the Number Series Task

Right hemisphere. The *z*-score analyses for the right hemisphere identified 3 DVs "normally" distributed before the removal of outliers; Oxy-Hb inferior PFC, Oxy-Hb superior PFC, and Oxy-Hb superior DLPFC. Scores identified outliers in the dataset for Oxy-Hb inferior DLPFC, Deoxy-Hb inferior DLPFC, and Deoxy-Hb superior DLPFC. Results identify no outliers for Deoxy-Hb inferior PFC nor Deoxy-Hb superior PFC. Removal of outlier scores was able to normalise scores for Oxy-Hb inferior DLPFC, Deoxy-Hb inferior DLPFC and Deoxy-Hb superior DLPFC. As discussed previously, the potential for transformations in this data set is limited to the use of inverse transformations owing to the mixture of positive and negative raw data scores. Inverse transformations did not render the two remaining regions of interest normally distributed. Nonparametric Kruskal Wallis tests on the two areas of interest not "normally" distributed did not show significant effects.

Initial correlations showed three high correlations for Oxy-Hb inferior DLPFC, with one of these being more than $r \pm .60$ and was consequently, removed from the list of MANOVA DVs. There were, therefore, five DVs in the MANOVA solution. The MANOVA showed no significant inter-group effects (Pillai's Trace F (< 1). There no univariate results or *post hoc* comparisons between groups. The analysis attempted a second MANOVA with Deoxy superior DLPFC removed due to some high inter-correlations, although these had all been $r < \pm .60$. The MANOVA result remained nonsignificant (Pillai's Trace $F < 1$). All univariate and *post hoc* results also remained nonsignificant. Table 23 shows the rCBF results for the right hemisphere on this task.

Table 23: *fNIRS* Right Hemisphere Oxy and Deoxy-Hb changes from baseline for the Number Series Task

Variable	**Controls (CO) *N* = 28**	**Heavy social drinkers (HSD) *N* = 20**	**Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22**	**Significance**	***Post-hoc*[1] *1.Control vs HSD 2.Controls vs HSDCC 3.HSD vs HSDCC***
Oxy-Hb Right Inferior PFC	-.036 (5.638)	.484 (5.664)	1.578 (4.867)	*F* (2, 64) =.604, *P*=.550,ηp^2= .018	*1. n.a 2. n.a 3. n.a*
Deoxy Right Inferior PFC	-1.593 (3.850)	-1.1632 (3.607)	.421 (2.298)	*H* [2, *N* = 70] = 4.516 *P* = .105	*1. n.a 2. n.a 3. n.a*
Oxy Right Superior PFC	-.065 (4.195)	-.979 (4.619)	-.5439 (4.600)	*F* (2, 64) = .555, *P*=.577,ηp^2=.017	*1. n.a 2. n.a 3. n.a*
Deoxy Right Superior PFC	-.997 (3.805)	-2.132 (3.876)	-.285 (2.754)	*H* [2, *N* = 70] = 3.965, *P* = .138	*1. n.a 2. n.a 3. n.a*
Oxy Right Inferior DLPFC	1.528 (4.479)	1.906 (5.710)	.065 (4.763)	*F* (2, 64) = 6.889, *P*=.002,ηp^2= 177	*1. n.a 2. n.a 3. n.a*
Deoxy Right Inferior DLPFC	-.764 (2.654)	-.583 (4.109)	-1.190 (2.797)	*F* (2, 64) = .347, *P*=.708,ηp^2= .010	*1. n.a 2. n.a 3. n.a*
Oxy Right Superior DLPFC	.723 (3.937)	1.730 (4.111)	.475 (4.630)	*F* (2, 64) = .252, *P*=.778,ηp^2= .008	*1. n.a 2. n.a 3. n.a*

Deoxy Superior DLPFC	Right	-.138 (2.458)	-.508 (3.977)	-.302 (2.612)	Omitted from Analysis	*1. n.a* *2. n.a* *3. n.a*

[1] All *Post-Hoc* analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .01$

Left hemisphere. The only region of interest for the left hemisphere "normally" distributed before the removal of outliers was the Oxy-Hb inferior PFC. The study identified and removed outliers for Oxy-Hb superior DLPFC and Oxy-Hb superior PFC. The analysis also removed outliers for Deoxy-Hb superior PFC. After the removal of outliers, only Oxy-Hb inferior PFC and Oxy-Hb inferior DLPFC had normal distributions. After inverse transformations, only Oxy superior PFC became "normally" distributed. The Kruskal Wallis test on the ROIs excluded from the MANOVA showed no significant inter-group effects. Subsequent correlations showed that Oxy-Hb sup PFC had to be removed from the model due to a score above $r \pm .60$. The MANOVA was not significant with Pillai's Trace $F < 1$. Neither of the univariate results was substantial, as were none of the *post hoc* comparisons. Table 24 shows the rCBF results for the left hemisphere on this task.

Table 24: *fNIRS* Left Hemisphere Oxy and Deoxy-Hb changes from baseline for the Number Series Task

Variable	Controls (CO) *N* = 28	Heavy social drinkers (HSD) *N* = 20	Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22	Significance	*Post-hoc*[1] *1.Control vs HSD 2.Controls vs HSDCC 3.HSD vs HSDCC*
Oxy-Hb Left Inferior PFC	-.036 (5.638)	.484 (5.664)	1.578 (4.867)	*F* (2, 64) =1.420, *P*=.250,ηp^2= .047	*1. n.a* *2. n.a* *3. n.a*
Deoxy Left Inferior PFC	-1.593 (3.850)	-1.163 (3.607)	.421 (2.298)	H [2, N = 70] =.290, P = .865	*1. n.a* *2. n.a* *3. n.a*
Oxy Left Superior PFC	-.065 (4.195)	-.979 (4.619)	-.543 (4.600)	Omitted from analysis	*1. n.a* *2. n.a* *3. n.a*
Deoxy Left Superior PFC	-.997 (3.805)	-2.132 (3.876)	-.285 (2.754)	*H* [2, *N* = 70] = 2.492, *P* = .288	*1. n.a* *2. n.a* *3. n.a*
Oxy Left Inferior DLPFC	1.528 (4.479)	1.906 (5.710)	.065 (4.763)	*F* (2, 64) =.729, *P*=.913,ηp^2= .003	*1. n.a* *2. n.a* *3. n.a*
Deoxy Left Inferior DLPFC	-.764 (2.654)	-.583 (4.109)	-1.190 (2.797)	*H* [2, *N* = 70] = .489, *P* = .783	*1. n.a* *2. n.a* *3. n.a*
Oxy Left Superior DLPFC	.723 (3.937)	1.730 (4.111)	.475 (4.630)	*H* [2, *N* = 70] = .250, *P* = .882	*1. n.a* *2. n.a* *3. n.a*

Deoxy	Left	-.138	-.508	-.302	*H* [2, *N* = 70] =	*1. n.a*
Superior		(2.458)	(3.977)	(2.612)	1.113, *P* = .573	*2. n.a*
DLPFC						*3. n.a*

[1] All *Post-Hoc* analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .01$

*f*NIRS analysis for the N-Back

Before presenting results from the N-Back, the researcher made an "*a-priori*" decision to combine the different levels of the task into one analysis due to recording anomalies which became apparent in the study of the data.

Right hemisphere. With regards to the analysis of the right hemisphere, the *Z*-score analyses identified outliers on all of the DV's for one participant, which may have been due to a technical fault in recording the data. Subsequent removal of these scores rendered Oxy-Hb inferior PFC, Oxy-Hb superior PFC, Oxy-Hb inferior DLPFC, Oxy-Hb superior DLPFC, and Deoxy-Hb superior DLPFC normally distributed. Inverse transformations for the three remaining variables failed to normalise them. Nonparametric analyses revealed that none of these analyses was significant intergroup differences. Due to a high correlation, results removed Oxy-Hb superior DLPFC from the MANOVA model. A separate univariate ANOVA did not show a significant intergroup effect for this variable. The MANOVA did not show a significant inter-group impact (Pillai's Trace F (8, 128) = 1.376, *ns*.) and none of the univariate analyses showed a significant inter-group effect. Table 25 shows the rCBF results for the right hemisphere on this task.

Table 25: *fNIRS* Right Hemisphere Oxy and Deoxy-Hb changes from baseline for the N-Back Task

Variable	**Controls (CO) *N* = 28**	**Heavy social drinkers (HSD) *N* = 20**	**Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22**	**Significance**	***Post-hoc*[1] *1.Control vs HSD 2.Controls vs HSDCC 3.HSD vs HSDCC***
Oxy-Hb Right Inferior PFC	2.276 (17.093)	1.023 (5.583)	-1.602 (5.720)	F (2, 64) =.301, P=.585,ηp^2= .005	*1. n.a 2. n.a 3. n.a*
Deoxy Right Inferior PFC	3.980 (15.328)	2.139 (4.640)	-.609 (3.340)	H [2, N = 70] = .4.083, P = .091	*1. n.a 2. n.a 3. n.a*
Oxy Right Superior PFC	2.147 (13.812)	1.320 (6.192)	.4193 (4.926)	F (2, 64) =.008, P=.929,ηp^2= .000	*1. n.a 2. n.a 3. n.a*
Deoxy Right Superior PFC	3.619 (14.164)	3.652 (5.538)	.397 (3.375)	H [2, N = 70] = 3.536, P = .171	*1. n.a 2. n.a 3. n.a*
Oxy Right Inferior DLPFC	2.688 (21.785)	-.130 (6.859)	1.180 (6.078)	F (2, 64) =.729, P=.913,ηp^2= .003	*1. n.a 2. n.a 3. n.a*
Deoxy Right Inferior DLPFC	4.583 (16.702)	1.838 (4.585)	1.703 (3.909)	H [2, N = 70] = .983, P = .983	*1. n.a 2. n.a 3. n.a*
Oxy Right Superior DLPFC	.967 (15.394)	-1.310 (4.581)	-1.196 (5.201)	F (2, 64) =.413, P=.652,ηp^2= .013	*1. n.a 2. n.a 3. n.a*

Deoxy	Right	2.912	2.464	.100	F (2, 64) =4.332,	*1. n.a*
Superior		(13.931)	(4.545)	(3.639)	P=.054,ηp^2= .062	*2. n.a*
DLPFC						*3. n.a*

[1] All *Post-Hoc* analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .01$

Left hemisphere. Analysis of the data from the left hemisphere revealed normal score distribution for Oxy-Hb inferior PFC, Oxy-Hb inferior DLPFC, and Deoxy-Hb inferior DLPFC. The *Z-score'*s indicated outliers for Deoxy-Hb inferior DLPFC, Deoxy-Hb superior DLPFC, Oxy-Hb superior PFC, Deoxy-Hb superior PFC, and Oxy-Hb inferior DLPFC. Inverse transformations were able to normalise the following variables; Deoxy-Hb superior PFC, Oxy-Hb superior DLPFC, and Deoxy-Hb superior DLPFC. The analysis used a nonparametric alternative for the two variables not "normally" distributed, with neither variable showing a significant inter-group difference.

Correlational analysis before the MANOVA indicated that the correlation between Deoxy-Hb inferior DLPFC and Oxy-Hb inferior DLPFC was very high, but just below the threshold of $r > .70$ (r (67) = .693 $P < .000$, two-tailed). The MANOVA solution was therefore tested firstly with both of these variables, and then with one of them removed. Results for the six-variable MANOVA solution approached significance (Pillai's Trace F (12, 120) = 1.720, P = .071, η_p^2 = .147). With regards to the five variable MANOVA, this was conducted following the removal of the variable Oxy-Hb inferior DLPFC, as this variable tended to have higher correlations with the other variables than Deoxy-Hb Inferior DLPFC. The result of the five variable MANOVA solution was now significant (Pillai's Trace F (10, 122) = 1.996 P = .039, η_p^2 = .141). Although none of the univariate analyses was significant against the revised alpha level of $P \leq .01$, the Deoxy-Hb Superior PFC came the closest (F (2, 64) = 3.206, P = .047, η_p^2 = .091), followed by Oxy-Hb superior DLPFC (F (2, 64) = 2.795, P = .069, η_p^2 = .080). The family-wise alpha level for the univariate analyses was $P \leq .049$. Adjustment of the alpha level calculated using EQ1 in Chapter 6 of this thesis, taken from Tabacjnick and Fidell (2014 P.312).

None of the inter-group comparisons was significant when evaluated against their revised alpha level of $P \leq .003$. The comparison between the HSD and the HSDCC groups for Deoxy-Hb superior PFC came the closest (P = .014, two-tailed), followed by the comparison between controls and the HSD group for Oxy-Hb superior DLPFC (P = .021, two-tailed). These are also the two variables which had shown the closest results to univariate significance. For the Deoxy-Hb superior PFC, the HSD group showed the most massive increase above baseline, and the HSDCC group the smallest increase. The controls were in the middle and did not significantly

differ from either group. For Oxy-Hb superior DLPFC, the control group showed a slight drop from baseline whilst the HSD group showed the most significant increase. The HSDCC group showed a small addition which did not significantly differ from the other groups. While these results are noteworthy, it is essential to reiterate that none of the univariate results or inter-group comparisons was significant. Table 26 shows the rCBF results for the left hemisphere on this task.

Table 26: *fNIRS* Left Hemisphere Oxy and Deoxy-Hb changes from baseline for the N-Back Task

Variable	Controls (CO) *N* = 28	Heavy social drinkers (HSD) *N* = 20	Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22	Significance	*Post-hoc*[1] *1.Control vs HSD 2.Controls vs HSDCC 3.HSD vs HSDCC*
Oxy-Hb Left Inferior PFC	2.276 (17.093)	1.0235 (5.583)	-1.602 (5.720)	F (2, 64) =1.289, P=.283,ηp^2= .093	*1. n.a* *2. n.a* *3. n.a*
Deoxy Left Inferior PFC	3.980 (15.328)	2.139 (4.640)	-.609 (3.340)	H [2, N = 70] = 3.091, P = .213	*1. n.a* *2. n.a* *3. n.a*
Oxy Left Superior PFC	2.147 (13.812)	1.320 (6.192)	.4193 (4.926)	H [2, N = 70] = 5.601, P = .061	*1. n.a* *2. n.a* *3. n.a*
Deoxy Left Superior PFC	3.619 (14.164)	3.652 (5.538)	.397 (3.375)	F (2, 64) =3.206, P=.047,ηp^2= .091	*1. n.a* *2. n.a* *3. n.a*
Oxy Left Inferior DLPFC	2.688 (21.785)	-.130 (6.859)	1.180 (6.078)	Omitted From Analysis	*1. n.a* *2. n.a* *3. n.a*
Deoxy Left Inferior DLPFC	4.583 (16.702)	1.838 (4.585)	1.703 (3.909)	F (2, 64) =.340, P=.713,ηp^2= .011	*1. n.a* *2. n.a* *3. n.a*
Oxy Left Superior DLPFC	.967 (15.394)	-1.310 (4.581)	-1.196 (5.201)	F (2, 64) =.586, P=.447,ηp^2= .009	*1. n.a* *2. n.a* *3. n.a*

Deoxy	Left					
Superior		2.912	2.464	.100	F (2, 64) = 2.795,	*1. n.a*
DLPFC		(13.931)	(4.545)	(3.639)	P = .069, η_p^2 =	*2. n.a*
					.080	*3. n.a*

[1] All *Post-Hoc* analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .01$

Given that the five variable MANOVA result had been significant, data analysis conducted a stepdown analysis to examine its validity. The results revealed that with Deoxy-Hb superior PFC as the dependent variable, Oxy-Hb superior DLPFC significantly interacted with the independent variable of the group (F (2, 19) = 3.934, P = .037, η_p^2 = .293). The analysis subsequently dropped Oxy Superior DLPFC from the model as this was the only other variable to approach a significant univariate result for intergroup differences. Rather than re-run the MANOVA with four DVs, the researchers decided to adopt a different approach. The approach would include three of the covariates identified in Chapter 5 as IVs: alcohol consumption in prior six months, No. of hours since last alcohol consumed, and alcohol onset age. As the DVs in these analyses, Deoxy-Hb superior PFC and Oxy-Hb superior DLPFC (both transformed variables) had a relatively small correlation. However, it was significant (r (67) = .270, P = .027, two-tailed). A revised alpha level set at $P \leq .025$ for each of two multiple linear regression (MLR) analyses which used them, respectively, as DVs. Neither of the MLRs was significant with $F < 1$ for Deoxy-Hb as the DV, and F (3,63) = 1,278, *ns*. for Oxy-Hb superior DLPFC as the DV. Curvilinearity in the unstandardised residuals was apparent in a scatterplot for the latter analysis so that the analysis performed the natural log transformations of the IVs. The resulting regression model remained nonsignificant ($F < 1$). Finally, estimated cannabis use in the past six months, which had not been included as an IV in the MLRs due to not being normally distributed, was not correlated with Oxy-Hb superior DLPFC (r_s (70) = .042, *ns.*). Still, a trend was apparent for Deoxy-Hb superior PFC (r_s (70) = -.217, P = .071, two-tailed).

*f*NIRS analysis for the COWAT

Right hemisphere. With regards to distribution scores for Oxy-Hb and Deoxy-Hb changes for the right hemisphere, results indicated normally distributed the scores for Oxy-Hb inferior PFC, Oxy-Hb superior PFC, Oxy-Hb inferior DLPFC and Oxy-Hb superior DLPFC. Subsequent z-score analyses showed that there were no outliers for Deoxy-Hb inferior and Deoxy-Hb superior PFC. However, the results identified *z*-scores greater than ± 3.29 for Deoxy-Hb inferior DLPFC and Deoxy-Hb superior DLPFC. Subsequent removal of outliers did not render any of the four Deoxy-Hb variables "normally" distributed. Besides data removal, inverse transformations made no difference to the distribution of these four variables, with or without the outliers. Subsequently, these variables were deemed unsuitable for inclusion in the MANOVA. Nonparametric Kruskal Wallis tests showed no significant effects on these four Deoxy-Hb variables. Correlations indicated that levels Oxy-Hb superior DLPFC had two high

positive correlations which were not more than $r = .70$. The subsequent MANOVA solution was nonsignificant with Pillai's Trace $F < 1$. Data analysis performed a further MANOVA with Oxy-Hb superior DLPFC omitted from the DVs, but, Pillai's Trace was once again nonsignificant $F < 1$. All univariate analyses were also nonsignificant. Table 27 shows the right hemisphere results for this task.

Table 27: *fNIRS* Right Hemisphere Oxy and Deoxy-Hb changes from baseline for the COWAT Task

Variable	**Controls (CO) *N* = 28**	**Heavy social drinkers (HSD) *N* = 20**	**Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22**	**Significance**	***Post-hoc*[1] *1.Control vs HSD 2.Controls vs HSDCC 3.HSD vs HSDCC***
Oxy-Hb Right Inferior PFC	.329 (8.274)	-.192 (6.324)	1.604 (7.386)	*F* (2, 67) = .328, *P* = .721, η_p^2 = .010	*1. n.a 2. n.a 3. n.a*
Deoxy Right Inferior PFC	-2.481 (6.550)	-1.696 (5.338)	.515 (3.777)	*H* [2, *N* = 70] = 3.614, *P* = .164	*1. n.a 2. n.a 3. n.a*
Oxy Right Superior PFC	-.010 (5.820)	-.882 (6.453)	-2.087 (5.676)	*F* (2, 67) = .747, *P* = .478, η_p^2 = .022	*1. n.a 2. n.a 3. n.a*
Deoxy Right Superior PFC	-2.773 (6.279)	-3.628 (6.442)	-1.356 (3.745)	H [2, N = 70] = .749, P = .688	*1. n.a 2. n.a 3. n.a*
Oxy Right Inferior DLPFC	1.491 (6.347)	1.392 (7.625)	-1.348 (6.967)	*F* (2, 67) = 1.234, *P* = .298, η_p^2 = .036	*1. n.a 2. n.a 3. n.a*
Deoxy Right Inferior DLPFC	-1.601 (3.549)	-1.227 (5.156)	-1.645 (4.513)	*H* [2, *N* = 70] = .773, *P* = .679	*1. n.a 2. n.a 3. n.a*
Oxy Right Superior DLPFC	1.667 (4.027)	1.898 (5.354)	.615 (5.967)	*F (2, 67) = .397, P = .674,* ηp^2 *= .012*	*1. n.a 2. n.a 3. n.a*

Deoxy	Right	-.739	-2.718	-.164	*H* [2, *N* = 70] =	*1. n.a*
Superior		(3.841)	(6.559)	(3.611)	4.454, *P* = .108	*2. n.a*
DLPFC						*3. n.a*

[1] All *Post-Hoc* analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .01$

Left hemisphere. Scores for Oxy-Hb and Deoxy-Hb changes within the left hemisphere found that results for Oxy-Hb inferior PFC, Deoxy-Hb inferior PFC, Oxy-Hb superior PFC and Oxy-Hb inferior DLPFC were all normally distributed. However, the *z*-score analysis found scores of greater than ±3.29 for Oxy-Hb inferior DLPFC, Oxy-Hb superior DLPFC, Deoxy-Hb superior DLPFC, and Deoxy-Hb inferior PFC. Deoxy-Hb inferior DLPFC had no outliers. Inverse transformations did not make normal any of the four variables above. Subsequent nonparametric analyses showed that none of these regions of interest had significant intergroup effects. Correlation analysis also indicated that there was no correlation over $r = \pm .60$. The subsequent MANOVA solution was nonsignificant, with Pillai's Trace F (8, 118) = 1.271, *ns*. The univariate result for Oxy inferior PFC did however approach significance, with F (2, 61) = 3.616, $P = .033$, $\eta_p^2 = .106$. The revised alpha level here for each univariate result was $P \leq .01$, calculated using EQ1 shown in Chapter 7 of this thesis (Tabachnick & Fidell, 2014 P.312). The family-wise alpha level was $P \leq .04$. Table 28 shows the left hemisphere results on this task.

Table 28: *fNIRS* Left Hemisphere Oxy and Deoxy-Hb changes from baseline for the COWAT Task

Variable	**Controls (CO) *N* = 28**	**Heavy social drinkers (HSD) *N* = 20**	**Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22**	**Significance**	***Post-hoc*[1] *1.Control vs HSD 2.Controls vs HSDCC 3.HSD vs HSDCC***
Oxy-Hb Left Inferior PFC	.329 (8.274)	-.192 (6.324)	1.604 (7.386)	*F (2, 67) = 3.616, P = .033, ηp² = .106*	*1. n.a 2. n.a 3. n.a*
Deoxy Left Inferior PFC	-2.481 (6.550)	-1.696 (5.338)	.515 (3.777)	*F (2, 67) = 1.182, P = .314, ηp² = .037*	*1. n.a 2. n.a 3. n.a*
Oxy Left Superior PFC	-.010 (5.820)	-.882 (6.453)	-2.087 (5.676)	*F (2, 67) = 1.544, P = .222, ηp² = .048*	*1. n.a 2. n.a 3. n.a*
Deoxy Left Superior PFC	-2.773 (6.279)	-3.628 (-3.628)	-1.356 (3.745)	*F (2, 67) = 1.220, P = .302, ηp2 = .038*	*1. n.a 2. n.a 3. n.a*
Oxy Left Inferior DLPFC	1.491 (6.347)	1.392 (7.625)	-1.348 (6.967)	*H* [2, *N* = 70] = .066, *P* = .967	*1. n.a 2. n.a 3. n.a*
Deoxy Left Inferior DLPFC	-1.601 (3.549)	-1.227 (5.156)	-1.645 (4.513)	*H* [2, *N* = 70] = 2.259, *P* = .323	*1. n.a 2. n.a 3. n.a*
Oxy Left Superior DLPFC	1.667 (4.027)	1.898 (5.354)	.615 (5.967)	*H* [2, *N* = 70] = 3.187, *P* = .203	*1. n.a 2. n.a 3. n.a*

Deoxy	Left	-.739	-2.718	-.164	*H* [2, *N* = 70] =	*1. n.a*
Superior		(3.841)	(6.559)	(3.611)	3.683, *P* = .159	*2. n.a*
DLPFC						*3. n.a*

[1] All *Post-Hoc* analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .01$

With regards to the intergroup comparisons, the revised alpha level for these was $P \leq .003$, none of the comparisons was significant. However, the comparison between the control group and HSD with cannabis for Oxy-Hb inferior PFC approached significance ($P = .010$, two-tailed). The means for this fNIRS measure for this ROI in Table 29.

Table 29: Descriptive statistics for Oxy-Hb Change Left Inferior PFC during the VWM task

	N	Mean	SD
Control	2.1739	26	5.26487
HSD	.4610	19	7.20726
HSDCC	-3.0253	19	7.07569

Results indicated that the controls showed an increase in Oxy-Hb change relative to baseline, whilst the HSDCC group showed a decrease. To investigate this further multiple linear regression analysis was conducted with the Oxy-Hb left inferior PFC. The study entered scores as the DV, and the following consumption variables as independent variables; Alcohol consumption in the prior six months, number of hours since last alcohol consumed and Alcohol onset age. The alcohol-related variables were entered hierarchically, based on their correlation with the DV, in Table 30.

Table 30: Sequence of IV inclusion for the Regression Model

Model	IV
1	Hours since last alcoholic drink
2	Hours since last alcoholic drink: Alcohol consumed the previous six months (units)
3	Hours since last alcoholic drink: Alcohol consumed the previous six months (units): Age of first alcohol use in years

Results for the MLR are in tables 31 and 32 and show that Oxy-Hb changes from baseline in the left inferior PFC with the group variables entered in all of the models 1-3 were nonsignificant. The residuals showed no evidence of heteroscedasticity or curvilinearity and normally distributed. Spearman correlation showed a significant negative correlation between

lifetime cannabis use and the Oxy-Hb left inferior PFC change from baseline scores (r_s (64) = -305, P = .014, two-tailed). Data analysis repeated this correlation after adding a constant to the Oxy left inferior PFC change scores to remove the negative values, to clarify our interpretation of this result. This correlation result was the same as the original without the use of the constant. Therefore, higher estimated use of cannabis was correlated with lower levels of Oxy-Hb in the left inferior PFC during the performance of the verbal working memory task (the COWAT). Results did not relate alcohol consumption variables to Oxy-Hb changes in this ROI.

Regarding task performance data, there were no cannabis-related effects on this task. However, the estimated amount of cannabis use in the previous six months is the only variable for which a full data set exists because, for non-users, entered a score of 0. Inevitably, this makes the variable highly skewed.

Table 31: Summary of regression analysis for Oxy-Hb change in the Left inferior PFC and predictors.

Model	R^2	R^2 change	*F* change	df1	df2	*Sig F* change
1	.008	.008	.518	1	62	.474
2	.016	.008	.483	1	61	.490
3	.021	.005	.297	1	60	.587

Table 32: ANOVA for Oxy-Hb change in the Left Inferior PFC and Predictors

Model	Component of variance	df	MS	*F*	Sig.
1	Regression	1	23.461	.518	.474[b]
	Residual	62	45.251		
	Total	63			
2	Regression	2	22.752	.499	.610[c]
	Residual	61	45.631		
	Total	63			
3	Regression	3	19.745	.428	.734[d]
	Residual	60	46.163		
	Total	63			

*f*NIRS response to the computerised grid task

Right hemisphere. Analysis of skewness and kurtosis values for the right hemisphere identified the Oxy-Hb inferior DLPFC and Oxy-Hb superior DLPFC as being normally distributed. Removal of violations to *z*-score limits was necessary for both Oxy-Hb inferior PFC, Oxy-Hb

Superior PFC, and Deoxy-Hb superior DLPFC, and succeeded in rendering these measures distribution "normal". Concerning transformation procedures, only inverse transformations are permissible with fNIRS data due to the negative values. Inverse transformation of Deoxy-Hb inferior PFC, Deoxy-Hb superior PFC and Deoxy-Hb inferior DLPFC failed to normalise the distribution of these variables.

Before the MANOVA solution, results omitted Oxy-Hb superior DLPFC due to high correlations. A separate univariate ANOVA on this DV showed no intergroup effect ($F < 1$). Multivariate analysis also failed to find a significant between groups impact using the four DV's retained in the MANOVA model (Pillai's Trace $F < 1$). Nonparametric equivalents for the remaining dependent variables also showed no significant intergroup effect. Table 33 shows the right hemisphere results for this task

Table 33: *f*NIRS Right Hemisphere Oxy and Deoxy-Hb changes from baseline for the Computerised Grid Task

Variable	Controls (CO) *N* = 28	Heavy social drinkers (HSD) *N* = 20	Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22	Significance	*Post-hoc*[1] *1.Control vs HSD 2.Controls vs HSDCC 3.HSD vs HSDCC*
Oxy-Hb Right Inferior PFC	-.732 (8.107)	1.228 (12.944)	.494 (7.754)	*F (2, 67) = .255, P = .775,* $\eta p^2 = .008$	*1. n.a 2. n.a 3. n.a*
Deoxy Right Inferior PFC	-2.621 (6.431)	-1.021 (7.225)	.060 (4.081)	*H* [2, *N* = 70] = 3.405, *P* = .182	*1. n.a 2. n.a 3. n.a*
Oxy Right Superior PFC	.616 (5.522)	.634 (8.416)	-.116 (4.467)	*F (2, 67) = .107, P = .898,* $\eta p^2 = .003$	*1. n.a 2. n.a 3. n.a*
Deoxy Right Superior PFC	-2.255 (6.336)	-3.134 (7.058)	-.210 (2.745)	*H* [2, *N* = 70] = 2.860, *P* = .239	*1. n.a 2. n.a 3. n.a*
Oxy Right Inferior DLPFC	.407 (7.239)	1.582 (9.402)	-1.732 (7.853)	*F (2, 67) = .919, P = .404,* $\eta p^2 = .027$	*1. n.a 2. n.a 3. n.a*
Deoxy Right Inferior DLPFC	-1.982 (3.807)	-1.422 (5.433)	-2.225 (4.680)	*H* [2, *N* = 70] = .207, *P* = .902	*1. n.a 2. n.a 3. n.a*
Oxy Right Superior DLPFC	.984 (5.103)	2.683 (7.352)	.481 (6.932)	*F (2, 67) = .682, P = .509,* $\eta p^2 = .020$	*1. n.a 2. n.a 3. n.a*

Deoxy	Right	-1.423	-3.083	-.931		*1. n.a*
Superior		(4.976)	(7.630)	(4.241)	*F (2, 67) = .829, P*	*2. n.a*
DLPFC					*= .441, ηp2 = .024*	*3. n.a*

[1] All *Post-Hoc* analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .01$

Left hemisphere. Analysis of skewness and kurtosis scores for Oxy-Hb and Deoxy-Hb for the left hemisphere indicated that the raw scores for Oxy-Hb inferior PFC, Deoxy-Hb superior PFC and Oxy-Hb inferior DLPFC were all normally distributed. Removal of outliers for Deoxy-Hb inferior DLPFC, Deoxy-Hb inferior PFC, Oxy-Hb superior DLPFC, and Deoxy-Hb Superior DLPFC failed to normalise these scores. There were no outliers for Oxy-Hb superior PFC. None of the inverse transformations rendered any of the variables "normally" distributed. MANOVA for the raw scores of the three "normally" distributed variables was nonsignificant for an intergroup effect with Pillai's Trace $F < 1$. None of the univariate results or intergroup comparisons was significant. Nor were the scores for the Kruskal Wallis analyses of the remaining five variables. Table 34 shows the left hemisphere results for this task.

Table 34: *f*NIRS Left Hemisphere Oxy and Deoxy-Hb changes from baseline for the Computerised Grid Task

Variable	**Controls (CO) *N* = 28**	**Heavy social drinkers (HSD) *N* = 20**	**Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22**	**Significance**	***Post-hoc*[1] *1.Control vs HSD 2.Controls vs HSDCC 3.HSD vs HSDCC***
Oxy-Hb Left Inferior PFC	-.732 (8.107)	1.228 (12.944)	.494 (7.754)	*F (2, 67) = 1.101, P = .339, ηp²* = *.035*	*1. n.a 2. n.a 3. n.a*
Deoxy Left Inferior PFC	-2.621 (6.431)	-1.021 (7.225)	.060 (4.081)	*H* [2, *N* = 70] =1.559, *P* = .459	*1. n.a 2. n.a 3. n.a*
Oxy Left Superior PFC	.616 (5.522)	.634 (8.416)	-.116 (4.467)	*H* [2, *N* = 70] = 3.267, *P* = .195	*1. n.a 2. n.a 3. n.a*
Deoxy Left Superior PFC	-2.255 (6.336)	-3.134 (7.058)	-.210 (2.745)	*H* [2, *N* = 70] = 1.014, *P* = .602	*1. n.a 2. n.a 3. n.a*
Oxy Left Inferior DLPFC	.407 (7.239)	1.582 (9.402)	-1.732 (7.853)	*H* [2, *N* = 70] = 3.672, *P* = .159	*1. n.a 2. n.a 3. n.a*
Deoxy Left Inferior DLPFC	-1.982 (3.807)	-1.422 (5.433)	-2.225 (4.680)	*F (2, 67) = .919, P = .291, ηp²* = *.040*	*1. n.a 2. n.a 3. n.a*
Oxy Left Superior DLPFC	.984 (5.103)	2.683 (7.352)	.481 (6.932)	*H* [2, *N* = 70] = 2.748, *P* = .253	*1. n.a 2. n.a 3. n.a*

Deoxy	Left	-1.423	-3.083	-.931	*F (2, 67) = 1.295,*	*1. n.a*
Superior		(4.976)	(7.630)	(4.241)	*P = .969, ηp²* =	*2. n.a*
DLPFC					*.001*	*3. n.a*

[1] All *Post-Hoc* analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .01$

*f*NIRS response to the Wisconsin card sorting task

Right hemisphere. Preliminary analyses indicated the normal distribution of scores for Oxy-Hb inferior PFC, Oxy-Hb superior PFC, and Oxy-Hb inferior DLPFC without the removal of outliers. Subsequent *z*-score analysis for the remaining regions failed to find outliers for Deoxy-Hb inferior PFC, Deoxy-Hb inferior DLPFC and Deoxy-Hb superior PFC. However, the research identified outliers for Oxy superior DLPFC and Deoxy superior DLPFC. Removal of the outliers normalised scores for Oxy-Hb superior DLPFC and Deoxy-Hb superior DLPFC. Finally, following inverse transformations, scores for Deoxy-Hb inferior DLPFC were rendered normally distributed. Neither of the two remaining variables showed significant group effects when subjected to a nonparametric Kruskal-Wallis analysis.

With regards to the multivariate analysis for the remaining variables, the correlational study indicated that Oxy-Hb superior DLPFC was positively correlated and subsequently removed from the analysis. Of the five remaining variables included in the initial MANOVA solution results showed that there was no significant inter-group effect with Pillai's Trace $F < 1$, and no significant univariate effects. Following the initial MANOVA, the correlational analysis indicated that Oxy-Hb inferior DLPFC had three positive correlations over $r = .50$, which although within limits set by Tabachnick and Fidell (2014), were nevertheless high. This variable was, consequently, removed for a second analysis. Once again, there was no significant inter-group effect (Pillai's Trace $F < 1$), and no significant univariate results. Results also indicated that the DV's Oxy-Hb superior DLPFC and Oxy-Hb inferior DLPFC were highly correlated. As Oxy-Hb inferior DLPFC showed a higher inter-group difference, data analysis conducted a univariate ANOVA on this DV. However, there was no significant inter-group effect ($F < 1$). Table 35 shows the right hemisphere results for this task.

Table 35: *fNIRS* Right Hemisphere Oxy and Deoxy-Hb changes from baseline for the WCST Task

Variable	**Controls (CO) *N* = 28**	**Heavy social drinkers (HSD) *N* = 20**	**Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22**	**Significance**	***Post-hoc*[1] *1.Control vs HSD 2.Controls vs HSDCC 3.HSD vs HSDCC***
Oxy-Hb Right Inferior PFC	-.434 (8.322)	-1.109 (6.475)	.407 (7.909)	*F (2, 67) = .186, P = .831, ηp² = .006*	*1. n.a 2. n.a 3. n.a*
Deoxy Right Inferior PFC	-3.203 (6.677)	-2.273 (5.339)	-.500 (4.792)	*H* [2, *N* = 70] = 2.274, *P* = .321	*1. n.a 2. n.a 3. n.a*
Oxy Right Superior PFC	1.638 (6.582)	-.688 (5.686)	.244 (5.322)	*F (2, 67) = 1.549, P = .221, ηp² = .048*	*1. n.a 2. n.a 3. n.a*
Deoxy Right Superior PFC	-2.297 (6.603)	-3.452 (6.572)	-.309 (2.636)	*H* [2, *N* = 70] = 2.233, *P* = .327	*1. n.a 2. n.a 3. n.a*
Oxy Right Inferior DLPFC	1.124 (7.633)	1.003 (7.751)	-1.136 (7.957)	*F (2, 67) = .662, P = .540, ηp² = .020*	*1. n.a 2. n.a 3. n.a*
Deoxy Right Inferior DLPFC	-1.861 (4.662)	-1.393 (5.343)	-2.154 (5.490)	*Omitted From Analysis*	*1. n.a 2. n.a 3. n.a*
Oxy Right Superior DLPFC	.360 (6.479)	.278 (5.650)	.054 (8.500)	*F (2, 67) = .721, P = .490, ηp² = .023*	*1. n.a 2. n.a 3. n.a*

Deoxy	Right	-1.874	-3.082	-.744	*F (2, 67) = 721, P*	*1. n.a*
Superior		(5.588)	(8.379)	(4.354)	*= .490, ηp² = .023*	*2. n.a*
DLPFC						*3. n.a*

[1] All *Post-Hoc* analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .01$

Left hemisphere. Results found normal distributions of scores without the removal of outliers for Oxy-Hb inferior PFC and Deoxy-Hb inferior DLPFC. Preliminary *z*-score analysis indicated that there were no outliers for Oxy-Hb inferior DLPFC and Deoxy-Hb inferior DLPFC. Additionally, scores did not "normally" distribute Oxy-Hb inferior PFC, Deoxy-Hb inferior PFC, Oxy-Hb superior DLPFC, Deoxy-Hb superior DLPFC, Oxy-Hb superior PFC and Deoxy-Hb superior PFC. Subsequent inverse transformations rendered Deoxy-Hb Superior DLPFC scores "normal". Kruskal Wallis nonparametric analyses were conducted on the five variables, not having a normal distribution, and showed that none of these variables showed a significant inter-group effect. For the MANOVA solution, the preliminary correlational analysis revealed no high correlations between the three variables selected. There was no significant multivariate inter-group effect (Pillai's Trace < 1) and no significant univariate effect. Table 36 shows the left hemisphere results for this task.

Table 36: *fNIRS* Left Hemisphere Oxy and Deoxy-Hb changes from baseline for the WCST Task

Variable	**Controls (CO) *N* = 28**	**Heavy social drinkers (HSD) *N* = 20**	**Heavy social drinkers with cannabis consumption (HSDCC) *N* = 22**	**Significance**	***Post-hoc*[1] *1.Control vs HSD 2.Controls vs HSDCC 3.HSD vs HSDCC***
Oxy-Hb Left Inferior PFC	1.659 (7.387)	-.900 (4.648)	.375 (7.542)	*F (2, 67) = 1.217, P = .303, ηp²* = .035	*1. n.a 2. n.a 3. n.a*
Deoxy Left Inferior PFC	.678 (5.418)	.923 (6.257)	-.796 (4.369)	*H* [2, *N* = 70] = 2.102, *P* = .350	*1. n.a 2. n.a 3. n.a*
Oxy Left Superior PFC	.060 (7.997)	-2.130 (8.059)	-3.576 (8.892)	*H* [2, *N* = 70] = 1.229, *P* = .541	*1. n.a 2. n.a 3. n.a*
Deoxy Left Superior PFC	-.169 (8.170)	-3.447 (8.841)	-1.631 (7.596)	*H* [2, *N* = 70] = .711, *P* = .701	*1. n.a 2. n.a 3. n.a*
Oxy Left Inferior DLPFC	-3.916 (15.005)	-.364 (7.500)	-6.120 (13.764)	*H* [2, *N* = 70] = 1.635, *P* = .442	*1. n.a 2. n.a 3. n.a*
Deoxy Left Inferior DLPFC	-2.998 (7.334)	-1.275 (4.004)	-4.095 (6.603)	*F (2, 67) = .661, P = .520, ηp²* = .019	*1. n.a 2. n.a 3. n.a*
Oxy Left Superior DLPFC	.164 (12.518)	-1.905 (9.724)	-1.287 (14.133)	*H* [2, *N* = 70] = 2.393, *P* = .302	*1. n.a 2. n.a 3. n.a*

Deoxy Left	-.858	-1.621	-.299	*F (2, 67) = .537, P*	*1. n.a*
Superior	(8.120)	(4.776)	(7.809)	*= .587, ηp² = .016*	*2. n.a*
DLPFC					*3. n.a*

[1] All *Post-Hoc* analyses were evaluated as two-tailed against a Bonferroni adjusted alpha level of $P \leq .01$

Discussion

This chapter aimed to investigate differences in rCBF changes from baseline as they pertain to cognitive task performance. Results found a significant multivariate effect between groups in the left hemisphere during the performance of the N-Back task (Gazzaniga et al., 2009). Still, there were no univariate effects or significant *post hoc* comparisons. A trend was noted in the superior PFC for the HSD group to have a more substantial increase in Deoxy-Hb than the HSDCC group during task performance. Similarly, for HSD participants to show the rise in Oxy-Hb in the superior DLPFC compared to a decrease from the baseline established by the controls, both of these trends could be consistent with more effortful cognition required by the HSD group than the other group in these respective comparisons (Roberts & Montgomery, 2015). These results will not be explored further concerning a potential relationship to substance consumption because of their lack of statistical significance. However, it is worth noting that as a language-based task using letters, it may not be surprising that the left hemisphere showed trends towards rCBF effects related to alcohol use, rather than the right hemisphere. There is evidence that computerised WM and EF tasks tend to elicit greater activation of structures in the left hemisphere compared to physical or paper tests (Fraser et al.,2020). This higher level of evoked activity could have contributed to the absence of inter-group effects in rCBF in the right hemisphere in the present study.

No significant between-group effects, either multivariate or univariate, were found for Go/No-Go task measuring inhibitory control (IC). The visuospatial working memory task (VSWM), or the Wisconsin Card Sorting Task (WCST) measuring executive set-shifting (ESS). Consequently, there was no evidence of more effortful cognition as a result of alcohol and cannabis consumption in these areas which draw upon the executive functions (EF) of working memory (WM: Baddeley, 2000b; Miyake et al., 2000, 2001). Similarly, the IR task used in this study also failed to show any significant inter-group effects concerning rCBF during task performance.

Although the Controlled Oral Word Association Task (COWAT: Stuss, 1998) of access to semantic long-term memory (Access) also failed to show any significant inter-group effects, there was a trend whereby the controls showed an increase in Oxy-Hb in the left inferior PFC during task performance, compared to a decrease shown by the HSDCC group. Lifetime

cannabis use estimates showed a significant negative correlation with Oxy-Hb changes in this ROI, while alcohol consumption showed no relationship to changes in this measure of rCBF. Lower levels of Oxy-Hb, therefore occurred with higher cannabis consumption and showing less effortful cognition in the performance of this task related to higher levels of cannabis use. Although the present data showed no effects in the DLPFC, decreased DLPFC activation on this task has previously related this to cannabis consumption (Aloi et al., 2018). It is important to note that there were also no inter-group effects in the present study on the performance measures for this task and that cannabis use has related to impaired Access functioning (Murphy et al., 2011). However, results could take the present to indicate that the HSDCC group maintained an adequate performance level with less effort. It is essential to note the robustness of EF and WM to compromised functioning arising from substance use (Briere et al., 2019), and the lack of sensitivity of tests of EF and WM to both subtle changes in performance ability and their ability to elicit rCBF changes in the neural substrates underpinning performance (Calabria et al., 2019). The diverse nature of these results reflects the indeterminate nature of results reported in the broader academic literature. (Morgan et al., 2016; Vandrey et al., 2013).

Concerning cannabis use, previous research has demonstrated that both THC and CBD may serve as neuroprotective agents against the effects of HSD (Toriño et al., 2010; Rubio et al., 2011). To date, there does not appear to have been any study of potential neuroprotective effects of cannabis use in the context of human alcohol consumption, and it is essential to emphasise that the present study did not test such a hypothesis. Nevertheless, the possibility of such an effect being present in the data obtained from the participant groups in the present study is one which should be acknowledged. The possible existence of such a neuroprotective effect could have contributed to the general lack of differences between the HSDCC group and the other two groups concerning both task performance and rCBF changes. This observation is particularly worth considering with the present sample as the HSDCC group had consumed more alcohol in the previous six months than the HSD group (see Chapter 5). It is also possible that the general lack of inter-group effects in rCBF could be a consequence of behavioural task overload, as reported by Robert and Montgomery (2015). This pattern is similar to the findings in brain imaging research of instances of cognitive overload where participants display a reduction in cortical activity as a result (Yun et al., 2010). This observation implies that testing

procedures in studies such as the present one need to spread out cognitive testing over a more extended period, despite the standard practice of rest breaks between tests.

The possible insensitivity of the tasks used to subtle changes in EF and WM and the protective effects of cannabinoids means the lack of significant inter-group effects could reflect the limitations of the use of *f*NIRS concerning brain activity related to EF and WM tasks. It is important to note that WM and EF tasks are not solely dependent upon PFC and DLPFC areas, but rather is a diffuse network of cortical and subcortical structures (Linden, 2007). The thalamus, for example, has been implicated in the processing of IC, IR EU and VSWM, with fMRI scans showing that the thalamus becomes hyper-stimulated in response to associated neurocognitive tests (Kulich et al., 2019). Furthermore, Troster (2019) reported that deep brain stimulation (DBS), where an electrical current applied to subcortical regions, including the thalamus, resulted in improved performance IC, IR, EU and VSWM. Therefore, before further conclusions about the relationship between brain activation in EF and WM tasks and the consumption of alcohol and cannabis can be made, more extensive studies of brain functioning are necessary for this field.

Finally, it is pertinent to consider the thesis inability to report upon the use of nicotine in this analysis. Indeed research has shown that nicotine consumption has an effect on rCBF in the DLPFC. Yuan et al. (2018) reported that cigarette smoking resulted in reduced hippocampal cell regeneration by 15% and reduced cortical activation of the DLPFC whilst engaged in WM tasks. The lack of data on cigarette consumption as a covariate of HSD and cannabis consumption posed a limitation to the analyses possible with the results presented in this chapter.

In conclusion, the only significant findings this chapter can report concern a relationship between cannabis use and lower Oxy-Hb levels in the left inferior PFC during a task concerning access to semantic long-term memory. Nonsignificant trends for the left superior PFC and left superior DLPFC, which indicated the presence of more effortful cognition related to alcohol use in performing an EU task suggest the need for further investigation. Results may relate to the general lack of significant effects reported in this chapter to the limitations of current tests

of EF and WM functioning. The possible protective effect of cannabinoids and the limits of *f*NIRS with regards to its inability to measure the activity of critical sub-cortical structures.

Chapter 9
General discussion.

Summary of main findings.

This thesis aimed to investigate differences in executive functioning (EF) and working memory (WM) task performance between the CO, HSD and HSDCC groups, together with concurrent task-related changes in rCBF measures. Whilst the literature around alcohol misuse has traditionally focused upon the cognitive effects of chronic alcohol addiction, research on the impact of HSD (binge drinking) is underdeveloped by comparison. Anstey et al. (2009), for example, was only able to find 15 publications suitable for inclusion in a meta-analysis on HSD induced deficits to WM. Research indicates that some binge drinkers use cannabis, and some do not (McKetin et al., 2014). Therefore, whilst the literature on HSD has grown since Montgomery et al. (2012), there are many matters unaddressed, and the issue of associated cannabis use is one of them. This lack of research serves as the foundation for the new contributions to knowledge which this thesis is making.

From the evidence presented in the literature reviews in chapters one and two, there is a significant degree of overlap in the psychobiological consequences of both HSD and cannabis consumption (Campanella et al ., 2013; Chanraud et al., 2009; Murphy, 2018). Their effects, with regards to neurotransmission and LTP, have been shown to impair WM, EF, and attendant behavioural impairments. These observations provide a basis for understanding the possible consequences of HSD cannabis smoking polydrug use. The meta-analytic studies conducted in chapters three and four found a marginally non-significant performance decrement for HSD cannabis-using participants in visuospatial functioning. But a more extensive and statistically significant decrement in studies of verbal memory.

Tables 37 and 38 summarise the significant intergroup differences and intergroup correlations from Chapter 5 to Chapter 8.

Table 37: summary of significant intergroup differences from Chapter 5 to Chapter 8.

Variable	Intergroup comparison results	Relevant chapter
Gender	The predominance of males in the sample	5
Depression	HSDCC > HSD HSDCC > CO	5
Premorbid IQ	HSDCC > HSD HSDCC > CO	5
Raven's Matrices IQ	HSDCC > HSD	5
Barratt Impulsivity: Attention Subscale	HSDCC > CO	5
Barratt Impulsivity: Motor Subscale	HSDCC > CO	5
Barratt Impulsivity: Self-control	HSDCC > CO	5
Barratt Impulsivity: Cognitive Complexity	HSD > CO	5
Barratt Impulsivity: Perseverance	HSD > CO HSDCC > CO	5
Barratt Impulsivity: Cognitive Instability	HSDCC > CO	5
Alcohol use frequency in the past three months	HSD > CO HSDCC > CO	5
Age of first use of alcohol (years)	CO > HSD HSD > HSDCC	5
Hours since last alcoholic drink	HSD > CO HSDCC > CO	5
Days since last alcoholic drink	HSD > CO HSDCC > CO	5
Times drinking per week	HSD > CO HSDCC > CO	5
Times drinking per month	HSD > CO HSDCC > CO	5
Times drinking per year	HSD > CO HSDCC > CO	5

Alcohol consumed the last six months (units)	HSD > CO HSDCC > CO	5
Go/No Go Error Rate for Horizontal Cues	*Sig.* A Main effect, but all inter-group comparisons *ns.*	7
Go/No-Go Number Overall Mean Reaction Time (in ms) for the go responses	HSDCC < HSD HSDCC < CO	7
Number Series Task Correct Pattern Recognition	CO > HSD	7
2-Back reaction time 3-Back Reaction time	*Sig.* A multivariate main effect, but no significant univariate effects or inter-group comparisons	7
	CO quicker RTs than HSD, but this was marginally *ns*. MLR showed six-month alcohol consumption to be significantly related to longer RTs	7
N-Back fNIRS	*Sig.* Multivariate inter-group effect for left hemisphere but no univariate results or group comparisons.	
VSWM Memory span	CO > HSDCC in comparisons following univariate ANCOVA. MLR showed cannabis use associated with smaller span scores. However, results related to six-month alcohol use and earlier onset of alcohol use to longer span scores.	7

Table 38: summary of significant intergroup correlations from Chapter 5 to Chapter 9

Variables	Correlational direction	Relevant chapter
Barratts Impulsivity: Attention Subscale and Alcohol units consumed in the past six months	Positive	5
Barratts Impulsivity: Attention Subscale and Onset age for alcohol use (years)	Negative	5
Barratts Impulsivity: Attention Subscale and Hours since last alcohol use	Positive	5
Barratts Impulsivity: Motor Subscale and Alcohol units consumed in the past six months	Positive	5
Barratts Impulsivity: Motor Subscale and Onset age for alcohol use (years)	Negative	5
Barratts Impulsivity: Motor Subscale and Hours since last alcohol use	Positive	5
Barratts Impulsivity: Self-control and Alcohol units consumed in the past six months	Positive	5
Barratts Impulsivity: Self-control and Onset age for alcohol use (years)	Negative	5
Barratts Impulsivity: Self-control and Hours since last alcohol use	Positive	5
Barratts Impulsivity: Cognitive Complexity and Alcohol units consumed in the past six months	Positive	5
Barratts Impulsivity: Cognitive Complexity and Onset age for alcohol use (years)	Negative	5
Barratts Impulsivity: Cognitive Complexity and Hours since last alcohol use	Positive	5
Barratts Impulsivity: Perseverance and Alcohol units consumed in the past six months	Positive	5
Barratts Impulsivity: Perseverance and Onset age for alcohol use (years)	Negative	5
Barratts Impulsivity: Perseverance and Hours since last alcohol use	Positive	5
Barratts Impulsivity: Cognitive Instability and Alcohol units consumed in the past six months	Positive	5
Barratts Impulsivity: Cognitive Instability and Onset age for alcohol use (years)	Negative	5
Barratts Impulsivity: Cognitive Instability and Hours since last alcohol use	Positive	5
HADS-D and alcohol units consumed in the previous six months	Negative	5
HADS-D and hours since last alcohol Use	Positive	5
HADS-A and onset age for alcohol use	Positive	5
3-Back reaction time and alcohol consumption in the last six months	Positive	7
VSWM span and where hours since last alcoholic drink	Positive	7
VSWM Span and Alcoholic units consumed in the past six months	Positive	7
VSWM Span age at first use of alcohol	Negative	7

Preliminary analysis of demographic variables from chapter five indicated a bias towards male participation in the study, making up 72% of the total sample. In terms of the group allocation, results suggest that there was a numerical bias towards males engaging in substance misuse (*N* = 14 for males in the HSD and *N* = 21) for the HSDCC group. Control group allocation, while still biased towards males (*N* = 16) was more balanced with regards to the number of females (*N* = 12). The analysis of background data also indicated that there was no significant difference in age between male and female participants. In terms of group allocation and participant age, however, HSD participants were older on average than participants in the CO and HSDCC groups. Still, a Kruskal Wallis analysis indicated that this difference was not significant.

The analyses in Chapter Five reported significant differences between the three groups in which the HSDCC group demonstrated higher levels of depression, and also higher levels of impulsivity compared to the HSD and CO groups. Studies have shown that both HSD and cannabis smoking population display more significant levels of depression compared to controls (Paljärvi et al., 2009; Asghar et al., 2019). This pattern of results, therefore, can be regarded as consistent with demographic findings from the relevant substance-using populations from within existing academic literature. However, results also indicate that the HSDCC group demonstrated higher premorbid IQ scores compared to either of the two other groups, and higher fluid IQ scores compared to the HSD group. Results from within the academic literature tend to report lower IQ scores in both HSD (Sjölund et al., 2016) and cannabis smoking populations (Mokrysz et al., 2016).

In terms of substance misuse indices, Chapter Five reported that while the HSD and HSDCC reported a higher rate of alcohol consumption compared to the CO group. The HSD and HSDCC do not differ on any alcohol use variable except onset age for which the HSDCC group was younger. Bivariate correlations with covariates representing alcohol consumption, showed that the depression scores were on the borderline of a significant negative correlation with the estimated number of alcohol units consumed in the previous six months. However, results did

show a stronger positive correlation with the number of hours since the last alcohol. Onset age for alcohol use had a positive correlation with the anxiety scores, which, whilst significant, was not robust. Results demonstrated a positive correlation for all indices of impulsivity and alcohol units consumed in the past six months and hours since the last alcoholic drink. These results are consistent with results from within the literature have reported that heavy social drinkers are more impulsive than non-bingers (Banca et al., 2016). The estimated alcohol use in the past six months and hours since last alcohol consumption showed universally positive correlations with the impulsivity sub-scales. Consequently, there had been long periods of abstinence for participants high in impulsivity. These findings would be consistent with the observation that binge drinking comprises short periods of excessive consumption, preceded and followed by periods of abstinence (McCaul et al., 2017).

Alcohol consumption in the previous six months showed a strong correlation with depression scores within the HSDCC group. Scores indicated that no correlation exists between hours since the participant last used cannabis and levels of depression. Within the HSDCC group (N = 22), there was no correlation reported for the age of first for cannabis use with the scores for depression, anxiety, any of the impulsivity sub-scales, premorbid IQ, or Raven's Matrices scores. However, the number of hours since the last use of cannabis had a relatively strong positive correlation with anxiety scores, indicating that anxiety was higher with more extended periods of abstinence. Research by Schuster et al. (2017) suggests this may be symptomatic of cannabis withdrawal, which increases anxiety levels. There was also no correlation for cannabis abstinence with any of the other background variables or substance consumption variables. The statistical power of the correlations with these two measures of cannabis use would, of course, limited by the relatively small number of participants in this group. However, taking values of '0' for cannabis consumption in the CO and HSD groups estimated cannabis consumed in the previous six months did show significant positive correlations with the impulsivity sub-scales for attention, motor performance, self-control, and mental instability. Consequently, for both alcohol and cannabis, impulsivity predicted higher consumption levels which again is in keeping with findings from the broader academic literature (VanderVeen et al. 2016; Lannoy et al., 2017).

With regards to the findings of chapters 7 and 8 on WM and EF performance, there were relatively few significant effects emerging from the data. The Go/No-Go task of IC did reveal quicker RTs for 'Go' responses for HSDCC participants compared to the other groups. However, the absence of significant effects on other performance measures for this task does not permit detailed speculation concerning whether results should interpret this as showing better (i.e. quicker) performance, or less attentive understanding. This pattern would be consistent with current (see Chapter 5) and previous findings (VanderVeen et al. 2016; Lannoy et al., 2017) regarding impulsivity in cannabis users. There was a significant multivariate effect for one of the error rate measures on this task. Still, there were no significant univariate effects or inter-group comparisons to shed light based on this result. However, the results for this task do suggest that IC functioning is an area worthy of further research concerning HSD and cannabis polydrug use. The *f*NIRS data on rCBF reported in Chapter 8 failed to show any significant effects for this task.

The number-series task of IR showed a significantly higher total of correct responses for the control participants compared to the HSD participants. While this would be consistent with the effects of HSD on essential brain areas in cognition (Campanella et al ., 2013; Chanraud et al., 2009; Weissenborn and Duka, 2003), the lack of any effects related to cannabis is not consistent with previous literature (Aloi et al., 2018; Broyd et al., 2016; Murphy, 2018). Given that the HSDCC group had higher alcohol consumption in the previous six months compared to the control group but not to the HSD group. The absence of any impairment in their performance relative to the controls raises the possibility of a neuroprotective effect of cannabinoids (Cabral & Jamerson., 2014; Sarne & Mechoulam, 2005) which would be worthy of further investigation. There were no significant effects on the *f*NIRS data on this task.

In terms of performance on the N-Back task, there was a significant multivariate effect across groups for the 2-Back condition. Still, there were no significant univariate effects or group comparisons. Although there were no inter-group effects for the 3-Back condition, multiple linear regression (MLR) showed alcohol consumption in the previous six months to be significantly related to longer RTs. The comparison between controls and HSD participants narrowly failed to be significant, with the control group showing faster times. The *f*NIRS data for this task showed a significant multivariate effect for the left hemisphere, but there were no

significant univariate effects or inter-group comparisons. Regrettably, recording errors had necessitated the combining of *f*NIRS data for this task across all four of its levels, as this may have obscured some effects which may have been significant at the respective groups. The results reported here are inconclusive, and also lack examination in terms of nicotine use which may also have impacted upon performance. Nevertheless, they do indicate that EU functioning is an area worthy of further research concerning the potential effects of HSD and cannabis polydrug use.

The VSWM task showed longer spans for control participants than the HSDCC group once data analysis had controlled covariates related to alcohol consumption. This control would be consistent with the findings of (Wareing et al. 2004) of a relationship between cannabis use and VSWM performance, and also other existing literature concerning the implications of cannabis use for cognitive functioning (Broyd et al., 2016; Murphy, 2018). However, contrary to prediction, alcohol consumption in the previous six months and earlier onset ages for alcohol use, were both related to longer VSWM span scores. These latter results are difficult to explain but may reflect an uneven distribution across the groups of the potentially confounding effects of impairments in brain activation and WM and EF performance arising from nicotine consumption (Gonzales et al. 2020; Nardone et al., 2020). As noted above, it was not possible to examine nicotine consumption as a covariate in this study due to an apparent misunderstanding of questions on this matter on the drug use questionnaire administered. The *f*NIRS results for the VSWM task showed no significant effects.

Concerning access to semantic long-term memory (Access), as measured by the COWAT, although there were no significant effects related to task performance. There was a significant negative correlation between the use of cannabis and Oxy-Hb changes in the left inferior PFC related to task performance. Although not significant, results found a trend for the control group to show an increase compared to baseline in Oxy-Hb in this ROI during task performance, compared to a decrease shown by the HSDCC group. Cannabis use has reported relation to impaired access to semantic long-term memory (Murphy et al., 2011). Despite the absence of performance differences between the groups in the present study, the finding of this left hemisphere effect warrants further investigation of the Access function of WM concerning HSD and cannabis polydrug use.

In conclusion, the WCST which failed to show any significant inter-group effects for either task performance or rCBF changes measured by fNIRS. Overall, the findings from the other areas of EF summarised above in this chapter, concerning inhibitory control, executive updating, visuospatial working memory, and access to semantic long-term memory, in addition to the results for inductive reasoning, provide grounds for suggesting that further research into these areas of functioning concerning the potential implications of HSD and cannabis polydrug use, would be justified. Nevertheless, a large majority of the analyses conducted in Chapters 7 and 8 showed no significant effects. Given the contrast of this absence of impact compared to the existing literature for alcohol and HSD (Campanella et al ., 2013; Chanraud et al., 2009; Weissenborn and Duka, 2003), and cannabis use (Aloi et al., 2018; Broyd et al., 2016; Murphy, 2018), the scarcity of significant effects may have been due to the limitations of the present study discussed below.

Limitations

The present study relied upon self-reports of alcohol and cannabis consumption, which are inevitably vulnerable to memory distortions, and also to the deliberate falsification of data for a variety of personal motives. Reliance upon self-reports in the literature is common practice, including the studies reviewed in Chapters 3 and 4 of this thesis. Lifetime estimates of consumption, and estimates of consumption in the previous six months, inevitably go beyond the ability of toxicological tests to verify, so that self-reports become the only source of data in many cases. Reliance upon self-reports also precludes the possibility of controlling for the differing strengths of cannabis possibly consumed, given the variability of cannabis potency found in black market supplies (Freeman et al., 2014; Hardwick & King, 2008). Its level of THC content determines the strength of a collection of cannabis. The lack of information regarding the potency of cannabis consumed means that the thesis can not address questions around the balance of neuroprotective and toxic effects linked to proportions of CBD and THC (Cabral & Jamerson., 2014; Sarne & Mechoulam, 2005). Once again, however, this limitation is shared with the studies reviewed in Chapters 3 and 4 of this thesis. Concerning alcohol consumption, the conversion of self-reports into estimated units of alcohol in the present study did provide some element of standardising the self-reported estimates of alcohol consumption.

The present study also has the limitation of having recruited participants from a student population, so that the thesis cannot consider the results as representative of a broader population of HSD and HSDCC consumers. Concerning the possible relationship between alcohol and cannabis-related effects on cognition in people who are older than the present sample and have differing levels of education, this is a limitation. Episodes of heavy drinking occur across all ages (Office for National Statistics, 2017) as does cannabis use (EMCDDA, 2019; Ganzer et al., 2016) so that the scope of the present study was reasonably limited in demographic terms from the outset.

The design of the present study used three groups to identify impaired cognitive functioning and differences in rCBF data which were related to alcohol and cannabis, respectively. The rationale was that if the HSD and HSDCC groups showed no differences from each other, but differed from the controls than the observed effect, researchers could attribute the effect to alcohol. Conversely, if the control group and HSD groups did not differ from each other, but differed from the HSDCC group, the results would attribute the observed effect to cannabis. It is clear from the literature that cannabis poses the possibility of a variety of potential products which may include neuroprotection (Cabral & Jamerson., 2014; Sarne & Mechoulam, 2005), and toxic damage to brain structures (Broyd et al., 2016; Ganzer et al., 2016; Murphy, 2018). The recruitment of the fourth group of cannabis users without HSD might have helped present a complete picture of the relationship between EF and WM functioning and cannabis and alcohol consumption patterns, respectively? In effect, the recruitment of such a group would have established a more explicit baseline against research could then compare the results of HSD and cannabis polydrug. The establishment of such baselines is an inherent and recurring issue in polydrug use research and has resource implications for the recruitment of adequate samples sizes (Taurah et al., 2014).

The present study used a cross-sectional design of pre-existing groups of HSD and HSDCC participants, plus controls. Murphy (2018) discusses the use of such methods in substance use research generally, which a response to the ethical, practical, and legal barriers to enforcing the consumption of alcohol, cannabis, and other drugs on participants before testing. The use of cross-sectional designs means that the only conclusion to be drawn is that of correlational relationships between substance consumption and cognitive functioning, as opposed to cause

and effect relationships. The present study, therefore, has this limitation, although its occurrence in the literature as a whole is not rare.

One significant limitation is the absence of data on nicotine use as the result of an apparent misunderstanding of questions on nicotine consumption in the drug use questionnaire administered to participants. Nicotine consumption results in lower grey matter density in the prefrontal cortex, cingulate gyrus, parietal lobe, cerebellum, thalamus, striatum and medial temporal lobe (Yuan et al., 2018). Nicotine has also resulted in impairments to the DLPFC liked to sensorimotor, emotional, and cognitive impairments (Levin et al. 2018). Nardone et al. (2020) reported nicotine consumption to be positively correlated with deficits to WM and EF in cannabis smokers, while Otto et al. (2020) reported that combinations of ethanol and nicotine resulted in decreased visuospatial working memory task performance. It is apparent therefore that the lack of data on tobacco and nicotine consumption as a covariate in the present study limited the analyses conducted into EF and WM functioning in the context of HSD and cannabis consumption, respectively.

One final limitation to the present study may is the nature of the measures of WM and EF used, and also of underlying brain activity as measured by fNIRS. It is the case that all of the tests used, as described in Chapter 6, were those identified by van Holst et al. (2011) as being the most suitable in their computerised form, for measuring these functions in a substance using population. Nevertheless, the literature does note the limitations to the sensitivity of existing neurocognitive tests to subtle changes in WM and EF in drug-using people (Fisk & Montgomery, 2011; Gauvin et al., 2016; Snyder et al., 2017). The present study would suffer from whatever limitations may exist to the sensitivity of the tests used. Still, many other tasks in the existing literature share these limitations. Concerning *f*NIRS, this constitutes a recording method for rCBF in the cerebral cortex (Roberts & Montgomery, 2015). Still, it is not capable of obtaining measures of activation in subcortical structures known to be important in cognitive functioning, such as the thalamus, hippocampus, and amygdala. Research has noted changes in the construction and functioning of these areas in reviews of the relationship between alcohol and cannabis consumption and cognitive functioning (Broyd et al., 2016; Murphy, 2018). Consequently, the inability of the present study to measure responses in these structures raises

the possibility that the thesis simply missed some acute effects of HSD and cannabis consumption.

Implications of the present findings

The primary area of practical implication arising from the findings concerns the development and application of diagnostic criteria for polydrug use. The results in Chapter 5 identified the HSDCC group as having a significantly higher profile than the other two groups concerning impulsivity and depression. Given the limitations of the current sample size, further research should seek to elaborate upon these findings for incorporation into revisions of DSM-5 (American Psychiatric Association, 2013), and guidelines for clinical practice produced for practitioners (e.g. Clinical Guidelines on Drug Misuse and Dependence Update, 2017). The development of interventions for curbing impulsivity, and for depression, for people with a substance use disorder involving HSD and cannabis use might be a possible development from the current findings after further research. Such work might include further investigation of IC functioning in people with HSD and cannabis use patterns of consumption.

These findings may inform health promotion initiatives by results concerning impulsivity and depression in HSD and cannabis use. The present findings come from a cross-sectional study and are essentially correlational. It is not possible to say from them if impulsivity and depression cause HSD and cannabis use, or if they are the consequence of such a pattern of substance use. Although these would be questions for further research, impulsive substance misuse, specifically HSD and cannabis smoking, have been described as an attempt at regulating negative emotions such as depression (Bo et al., 2016). The practical implications of such findings are that they highlight possible warning indicators for educators in schools and colleges to identify individuals who may be vulnerable to developing this pattern of substance use. In this regard, it is worth noting that Chapter 5 reported that the HSDCC group had an earlier onset age for alcohol use. The HSDCC group also had higher premorbid IQ than both other groups and higher fluid IQs than the HSD group. The combination of high impulsivity, depression, high IQ, and early onset of alcohol use may therefore present a set of warning indicators for those who work with young people, and who might be able to bring in, appropriate interventions promptly. An extensive literature already exists concerning the

harmful effects of early-onset alcohol use (Broyd et al., 2016; Schweinsburg et al., 2010). This literature is also present in cannabis use (Solowij & Battisti, 2008; Schweinsburg et al., 2005, 2008) which present a consistent picture of harm and dysfunction with which the present findings are consistent.

The general lack of significant findings for the tests of WM and EF necessarily limits the practical implications arising from the results in Chapters 7 and 8. In short, although there are indications that further research in some areas of functioning would be appropriate. The present results do not show a pattern of impairments suggesting that remedial interventions and the consideration of constraints on such things as using machinery and driving, need to be considered. The present findings are not however consistent with some other findings concerned with HSD and cannabis use (Broyd et al., 2016; Campanella et al ., 2013; Chanraud et al., 2009; Murphy, 2018).

Potential future Directions

In addition to the implications for further research and professional practice discussed in the previous section, there were relatively few significant effects in the findings reported in Chapters 7 and 8 concerning WM and EF. The results which did emerge do suggest the utility of further research in the areas of inhibitory control, inductive reasoning, executive updating, visuospatial working memory, and access to semantic long-term memory, concerning the potential implications of HSD and cannabis polydrug use on functioning. Future studies will require careful and detailed attention to the effects of potential covariates such as tobacco and nicotine consumption (Nardone et al., 2020; Otto et al., 2020) as well as other drugs of misuse, to control for their potentially confounding effects. As noted by Murphy er al., (2018), the field of cannabis and alcohol consumption research is dominated by animal studies, specifically with research conducted on rats. Therefore, there is a need for future scientific knowledge of the effects of cannabis and alcohol on human cognition to be based upon studies with human rather than animal participants.

Despite the evidence which exists for toxic effects linked to cannabis consumption (Murphy, 2018; Rochetti et al., 2013), the potential neuroprotective effects of cannabinoids (Cabral & Jamerson., 2014; Sarne & Mechoulam, 2005), including both THC and CBD, needs further investigation. Such an inquiry would present a fuller picture of the relationship between cannabis use and cognitive functioning. Concerning cannabinoid biomarkers given the high lipid solubility of THC, blood plasma estimates would be inappropriate as they would not provide an accurate measure of THC consumed. Hair follicle analysis with its ability to cover more extended periods would be a logical alternative (Mieczkowski et al. 1993).

The further development of tests which would be maximally appropriate for use in testing WM and EF in substance misusing populations is one area requiring further attention (Gauvin et al., 2016; Snyder et al., 2017). The development of these tests might also link them to conceptual products regarding the description and classification of WM and EF processes. Murphy et al. (2012) noted such issues concerning VSWM tests administered to users of ecstasy (MDMA). Rather than group all VSWM tests together in their meta-analyses, Murphy et al. separated trials into four different categories, such as those involved in tracking and locating stimuli, and reproducing complex figures, respectively. A further example was the report of Polderman et al. (2009) that the Stroop test of cognitive inhibition also drew upon semantic memory so that it was unclear what cognitive function the test analysed. The point for the present discussion is that more explicit conceptualisations of WM and EF processes will go together with better measurement, which will, in turn, enable a better picture of the implications of HSD and cannabis consumption for WM and EF to emerge.

A further avenue of research may include the relationship of relevant genetic variants to HSD and cannabis use effects on cognitive functioning. For example, the gene for the P450 2E1 liver enzyme is polymorphic, with the variant held by a particular individual determining the rate of metabolism of both alcohol and cannabis, and thus their bioavailability (Zakhari & Li, 2007; Watanabe et al., 2007). It is reasonable to assume that the bioavailability of alcohol and cannabis to the brain will be an essential variable mediating their effects on cognition and underlying brain activity. The incorporation of appropriate genetic testing into future research in this field would constitute a significant step forward.

In conclusion, Chapter 1 of this thesis highlighted the high levels of use across many societies of both alcohol and cannabis. The large number of people who may potentially be affected by the harmful consequences of HSD and cannabis use makes it essential that research in this field continues and receives the support it needs

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